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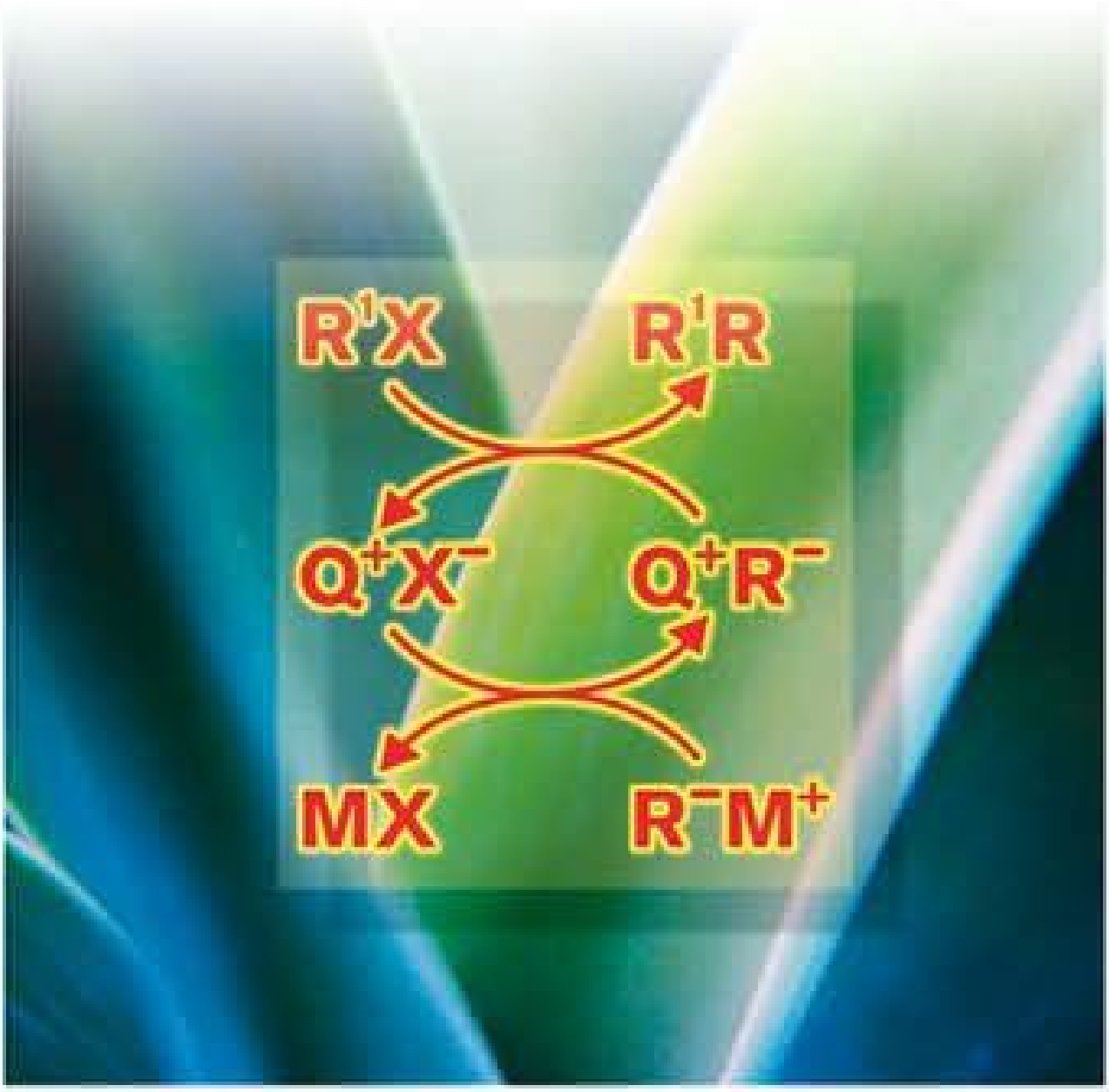
Asymmetric Phase Transfer Catalysis



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Preface

In contrast to the wide availability of phase-transfer reactions and processes using non-chiral phase-transfer catalysts, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has progressed rather slowly, despite the great importance of creating a new domain in modern asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetra-alkylammonium salts. Following the first meaningful discovery of *N*-(*p*-(trifluoromethyl)benzyl)cinchonidium bromide as chiral phase-transfer catalyst by the Merck group in 1984, various types of cinchona-alkaloid-derived chiral phase-transfer catalysts have been developed. The major applications of such catalysts include the enantioselective synthesis of amino acid derivatives by the asymmetric alkylation of glycine and other α-alkylamino acid derivatives. Although O'Donnell, in 1989, applied *N*-(benzyl)cinchoninium chloride and its cinchonidine derivative to the asymmetric synthesis of both enantiomers of α-alkylamino acid derivatives, research in this area subsequently made little progress for some time after these milestone reports. However, in 1997 a new class of cinchona alkaloid-derived catalysts bearing an *N*-anthracenylmethyl function, and developed independently by Corey and Lygo, opened a new era of asymmetric phase-transfer catalysis.

Two years later, in 1999, a totally new aspect on the design of chiral phase-transfer catalysts was reported, based on the use of non-cinchona-alkaloid derivatives. These structurally rigid, chiral spiro ammonium salts were introduced by using commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol as a new C_2-symmetric chiral phase-transfer catalyst, and successfully applied to the highly efficient, catalytic enantioselective alkylation of glycine Schiff base under mild phase-transfer conditions. The rational design of chiral binaphthyl-modified phase-transfer catalysts was relatively straightforward in comparison with cinchona-alkaloid-derived chiral phase-transfer catalysts, and was realized by fine-tuning the 3,3′-diaryl substituents of the chiral binaphthyl moiety. This allowed the systematic development of a variety of new – yet practical – asymmetric transformations under mild phase-transfer conditions, and inspired the further design of cinchona alkaloid-derived phase-transfer catalysts and other forms of chiral phase-transfer catalyst. Accordingly,

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major efforts towards this direction have recently resulted in notable achievements, whereby it has become feasible to perform a variety of enantioselective bond-formation reactions under mild phase-transfer-catalyzed conditions.

The aim of this book is to provide a concise and comprehensive treatment of this continuously growing field of catalysis, focusing not only on the design of the various types of chiral phase-transfer catalyst but also on the synthetic aspects of this chemistry. In addition, the aim is to promote the synthetic applications of these asymmetric phase-transfer reactions by giving solid synthetic evidence. Clearly, despite recent spectacular advances in this area, there is still plenty of room for further continuous development in asymmetric phase-transfer catalysis.

Kyoto, January 2008 *Keiji Maruoka*

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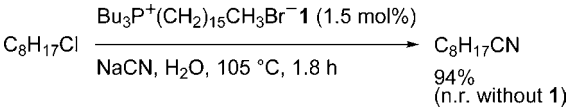
1
The Basic Principle of Phase-Transfer Catalysis and Some Mechanistic Aspects

Takuya Hashimoto and Keiji Maruoka

1.1
Introduction

In 1971, Starks introduced the term "phase-transfer catalysis" to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances located in different immiscible phases [1]. For instance, the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousand-fold by the addition of hexadecyltributylphosphonium bromide **1** as a phase-transfer catalyst (Scheme 1.1). The key element of this tremendous reactivity enhancement is the generation of quaternary phosphonium cyanide, which renders the cyanide anion organic soluble and sufficiently nucleophilic.



Scheme 1.1

Although this was not the first observation of the catalytic activity of quaternary onium salts, the foundations of phase-transfer catalysis were laid by Starks, together with Makosza and Brändström, during the mid to late 1960s [2]. Ever since that time, the chemical community has witnessed the steady growth of phase-transfer catalysis as a practical methodology for organic synthesis, featuring its simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations [3,4]. Nowadays, phase-transfer catalysis appears to be a prime synthetic tool, being appreciated not only in various fields of organic chemistry but also among widespread industrial applications.

Despite the development of phase-transfer catalysis in organic synthesis, the mechanistic aspects of phase-transfer catalysis remain obscure, due mainly to the

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difficulty of investigating biphasic systems and the many complex parameters that must be analyzed.

The aim of this chapter is to assist the reader to generate an intuitive understanding of the mechanism of asymmetric phase-transfer catalysis, together with a practical guide for the design of such processes. More detailed studies related to the physical and numerical aspects of phase-transfer catalysis may be consulted elsewhere [3].

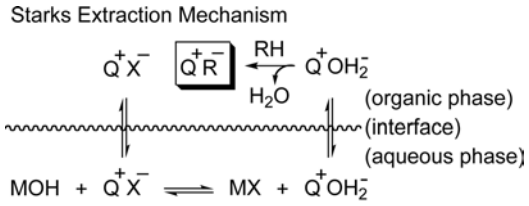
1.2 Inorganic Base-Promoted Activation of Acidic Organic Compounds

The representative reaction system applied in asymmetric phase-transfer catalysis is the biphasic system composed of an organic phase containing an acidic methylene or methine compound and an electrophile, and an aqueous or solid phase of inorganic base such as alkaline metal (Na, K, Cs) hydroxide or carbonate. The key reactive intermediate in this type of reaction is the onium carbanion species, mostly onium enolate or nitronate, which reacts with the electrophile in the organic phase to afford the product.

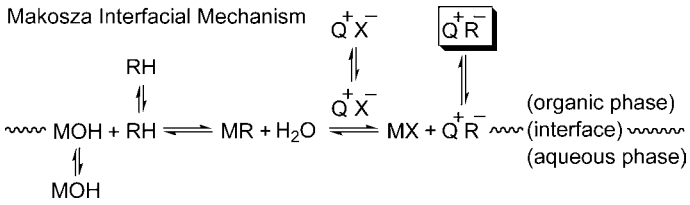
1.2.1 Generation of Reactive Onium Carbanion Species

The exact pathway for generating the reactive onium carbanion species remains the subject of controversy, typically among Starks extraction mechanism (Scheme 1.2) and the Makosza interfacial mechanism (Scheme 1.3).

In the Starks extraction mechanism, the phase-transfer catalyst moves back and forth across the organic and aqueous phases. The onium salt equilibrates with the inorganic base in the aqueous phase, and extracts hydroxide into the organic phase.



Scheme 1.2



Scheme 1.3

The onium hydroxide then abstracts hydrogen from the acidic organic compound to give the reactive intermediate Q^+R^-.

The advocated pathway of the interfacial mechanism is the first formation of metal carbanion at the interface of organic and aqueous phase in the absence of phase-transfer catalyst, followed by the extraction of the formed metal carbanion species from the interface into the organic phase by the action of phase-transfer catalyst.

Since asymmetric phase-transfer catalysts normally contain highly lipophilic chiral organic frameworks, and are reluctant to enter the aqueous phase, the Makosza interfacial mechanism seems plausible.

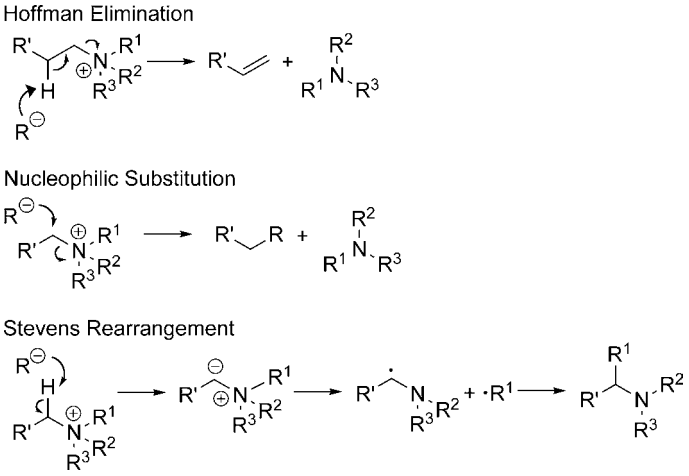
Clearly, the area of the interface and the basicity of the inorganic salt affect the amount of available onium carbanion. It should be also noted that an excessively lipophilic phase-transfer catalyst would hardly access the interface, and consequently the use of such a catalyst would result in an insufficient reaction.

1.2.2
Stability of the Onium Carbanion

The onium carbanion formed under phase-transfer conditions is unstable depending on the anion source, and in the absence of an electrophilic reaction partner, degradation of the accumulated onium carbanion in the organic phase may be observed. This is known to proceed via Hoffman elimination, nucleophilic substitution and/or Stevens rearrangement (Scheme 1.4) [4f,6,7]. The direct decomposition of onium salt, as influenced by the strong inorganic base at the interface, may be also operative.

1.2.3
Reactivity of the Onium Carbanion

Cation exchange from the metal cation to the onium carbanion improves the intrinsic reactivity of the latter due to formation of the "naked anion". At the same time, the



Scheme 1.4

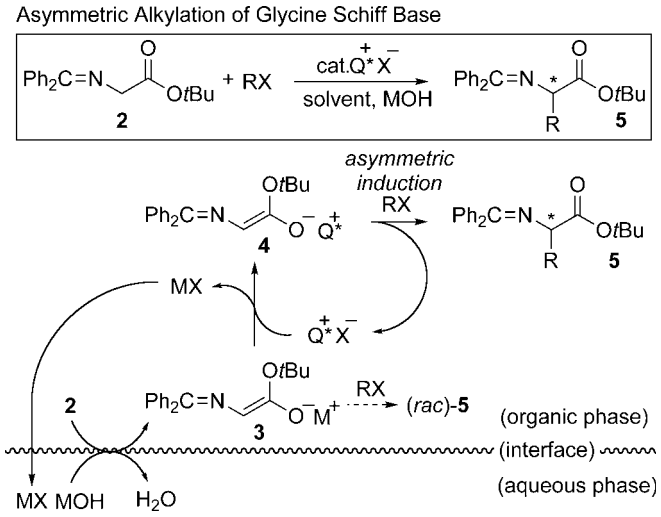
onium carbanion in the organic phase is less hydrated compared to the metal carbanion at the interface, which functions as another factor for an enhanced reactivity of the onium carbanion.

1.2.4
Nuclueophilic Substitution Reaction

(1.1)

The fate of the onium carbanion Q^+R^- incorporated into the organic phase depends on the electrophilic reaction partner. The most studied area in the asymmetric phase-transfer catalysis is that of asymmetric alkylation of active methylene or methine compounds with alkyl halides, in an irreversible manner. The reaction mechanism illustrated above is exemplified by the asymmetric alkylation of glycine Schiff base (Scheme 1.5) [8].

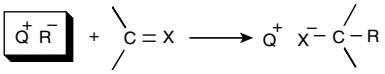
In the first step, glycine Schiff base **2** reacts with the inorganic base at the interface of two phases to give the metal enolate **3**, which remains at the interface due to its highly polar character. The metal enolate **3** then exchanges the cation to provide onium enolate **4**. The sufficiently lipophilic **4** then moves into the organic phase to react with alkyl halide. After the reaction, onium halide is regenerated and enters the next catalytic cycle. The key issue to be considered here is the possibility of product racemization and dialkylation. In this example, the basicity of the inorganic base and acidity of the substrate and product, as well as other reaction conditions, are carefully adjusted to circumvent this problem. It should be also noted that control of the *E*/*Z* geometry of the enolate is apparently critical to the asymmetric induction, although there is no clear evidence about which isomer is the actual reacting species in this case.



Scheme 1.5

An asymmetric S_N2' reaction and S_NAr reaction are included as other examples of this category.

1.2.5
Nucleophilic Addition to Electrophilic C=X Double Bonds

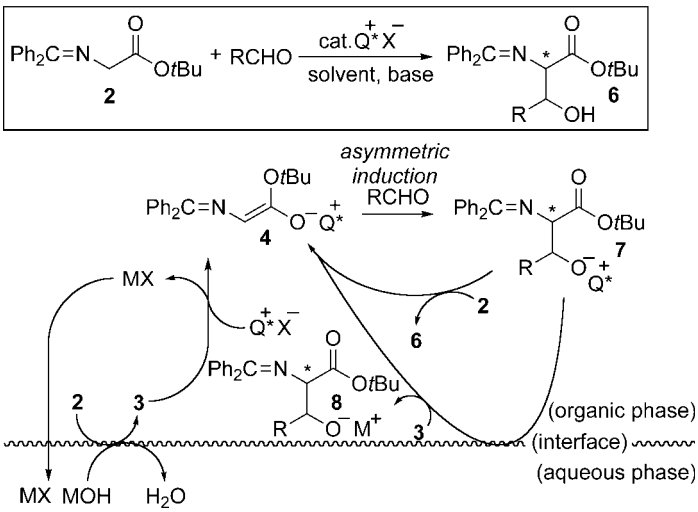


(1.2)

Unlike the nucleophilic substitution reactions which generate stable onium halide after the reaction, nucleophilic additions to electrophilic C=X double bonds (X=C, N, O) provide rather basic onium anion species as an initial product. If the anion is sufficiently stable under the reaction conditions, onium anion will then exchange the counter ion for the other metal carbanion at the interface to regenerate the reactive onium carbanion Q^+R^-. In another scenario, the basic onium anion may abstract the acidic hydrogen atom of the other substrate to provide Q^+R^- directly. Such a reaction system ideally requires only a catalytic amount of the base although, in general, a substoichiometric or excess amount of the base is used to lead the reaction to completion. An additional feature of this system is the substantial possibility of a retro-process at the crucial asymmetric induction step, which might be problematic in some cases.

The direct asymmetric aldol reaction under phase-transfer conditions is a representative example of this class of phase-transfer reaction, which is known to proceed with a catalytic amount of base and to include an undesired retro-process (Scheme 1.6) [9]. Here, the onium enolate **4** reacts with aldehyde in the organic

Direct Asymmetric Aldol Reaction of Glycine Schiff Base



Scheme 1.6

phase to give the onium alkoxide **7**, which may abstract the hydrogen from the other glycine Schiff base **2** to provide another reactive intermediate onium enolate **4** and the protonated aldol product **6**. It should be noted that this is not the only expected pathway, and there are complex equilibriums in this reaction system which, for reasons of clarity, not fully delineated below. The phase-transfer-catalyzed asymmetric Michael addition and the Mannich reaction are other typical examples which fall into this category.

1.3 Phase-Transfer-Catalyzed Addition of Anion Supplied as Metal Salt

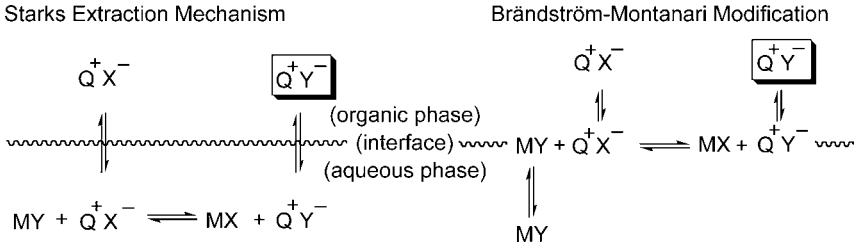
The common feature in the asymmetric phase-transfer catalysis introduced above is formation of the reactive onium carbanion from the inorganic base and active methylene or methine compounds, followed by extraction of the carbanion species as the onium salt from the interfacial area into the organic phase. Thus, both reagents normally remain in the organic phase. In the other category of asymmetric phase-transfer catalysis, the anion itself supplied as an aqueous solution or solid of its inorganic salt as the reaction partner, and the two reactants are strictly separated by the interface. In such a system, the anion is transferred gradually from the aqueous phase into the organic phase by the intervention of an onium salt.

With regards to the mechanism of the generation of onium anion, the Starks extraction mechanism and interfacial mechanism (Brändström–Montanari modification) are suggested (Scheme 1.7). As in the above-described case, the interfacial mechanism seems to be operative in the asymmetric phase-transfer catalysis.

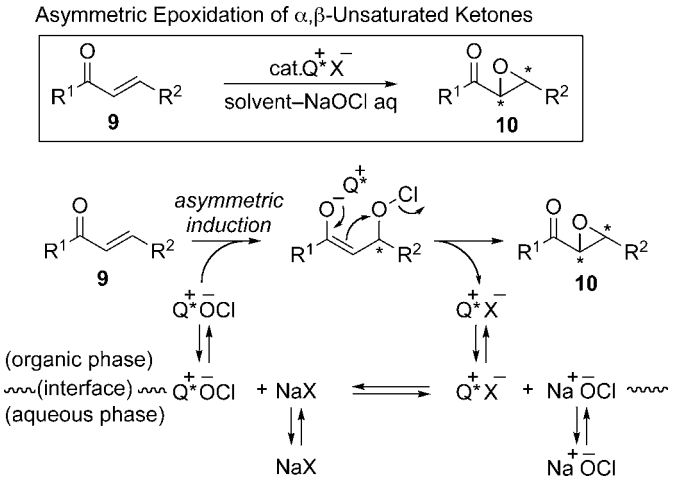
The reaction conditions are rather mild, so that the possibility of side reactions, such as catalyst decomposition, is considerably reduced. The major challenge associated with these reactions is an absence of prochirality in the anionic species. Namely, the chiral onium anion must discriminate the enantiotopic face of the distant electronically neutral reaction partner in the organic phase.

Asymmetric phase-transfer catalyzed oxidation of olefin using sodium hypochlorite or potassium permanganate as metal anion sources is the typical example of this category.

The asymmetric epoxidation of an α,β-unsaturated ketone, using sodium hypochlorite, is illustrated in Scheme 1.8 [10]. Hypochlorite is extracted as an onium



Scheme 1.7



Scheme 1.8

salt into the organic phase, and the onium hypochlorite then reacts with the ketone while recognizing its enantiotopic face to provide the optically enriched α,β-epoxy ketone.

1.4
Use of Crown Ether as Phase-Transfer Catalyst

Crown ether is the other important class of phase-transfer catalysts which critically differs from the onium salt, in that the whole inorganic salt is transferred into the organic phase. The reaction modes described above can generally be accommodated in such crown ether-catalyzed reactions, simply by replacing the onium cation by a metal cation complex of crown ether.

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2
Cinchona-Derived Chiral Phase-Transfer Catalysts for Amino Acid Synthesis

Takashi Ooi

2.1
Introduction

As long ago as the 16th century, quinine was extracted from the bark of the South America cinchona tree and used to treat fevers, especially malaria. Subsequently, cinchona alkaloids have enjoyed a long and rich history in medicine [1], and have also found numerous applications in organic chemistry, particularly in asymmetric catalysis, due to their attractive structural features and ready availability in both pseudoenantiomeric forms [2]. The first successful use of cinchona alkaloids for chiral phase-transfer catalysis was conducted by the Merck research group in 1984, who achieved the highly enantioselective methylation of phenylindanone derivative under organic-aqueous biphasic conditions in the presence of *N*-alkylated cinchonine [3]. This report certainly triggered the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral catalysts to create optically active organic molecules from prochiral substrates [4]. In this chapter, the fruitful applications of cinchona alkaloid-derived, monomeric chiral phase-transfer catalysts for the asymmetric synthesis of amino acids are described in a concise manner. Further details of the uses of cinchona-derived dimeric and polymeric phase-transfer catalysts are discussed in Chapter 3.

2.2
α-Amino Acid Synthesis

2.2.1
Monoalkylation of Schiff Bases Derived from Glycine

In 1989, O'Donnell and coworkers successfully utilized cinchona alkaloid-derived chiral quaternary ammonium salts for the asymmetric synthesis of α-amino acids using *tert*-butyl glycinate benzophenone Schiff base **1** as a key substrate [5]. The asymmetric alkylation of **1** proceeded smoothly under mild phase-transfer

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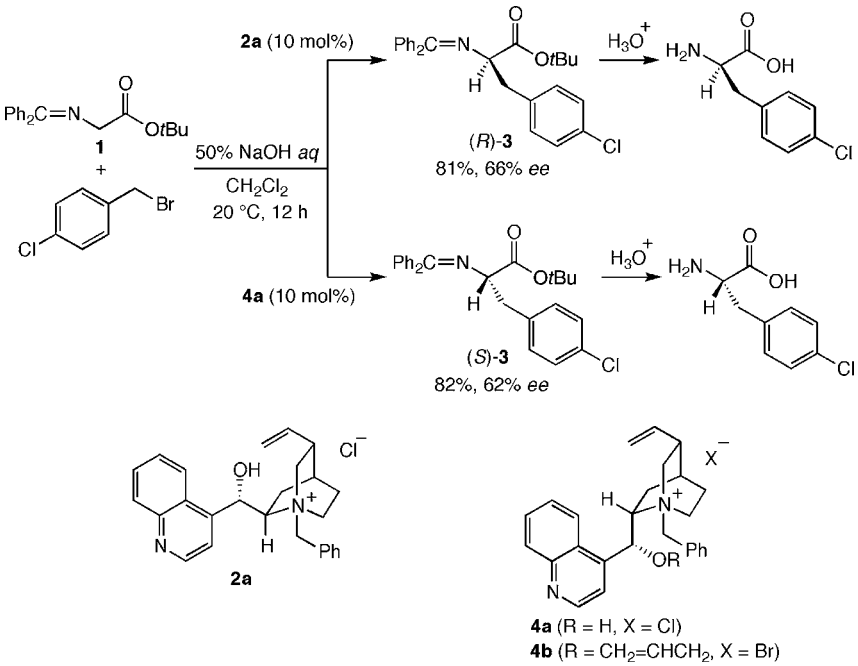
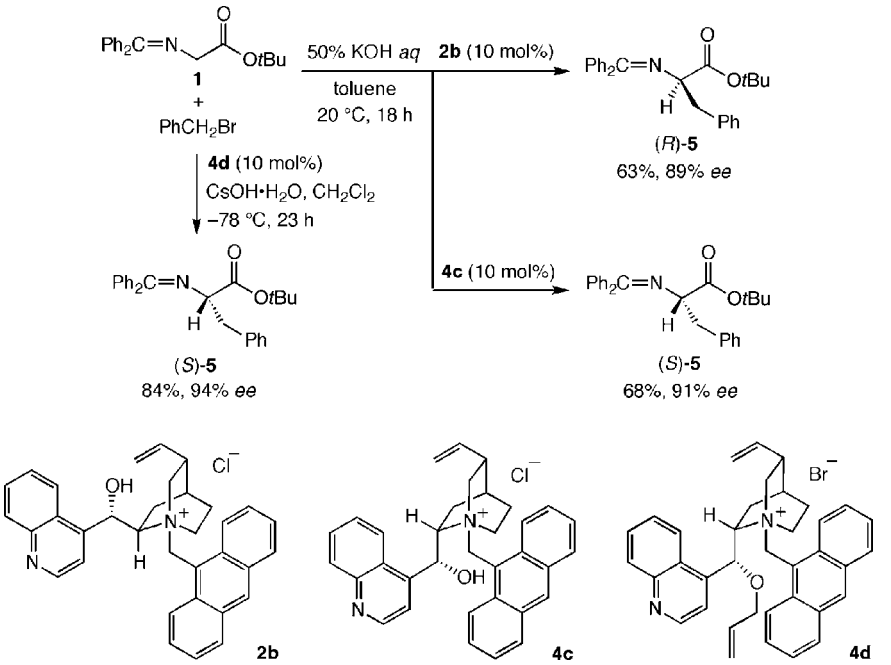


Scheme 2.1

conditions, with *N*-benzylcinchoninium chloride (**2a**) as a catalyst, to give the alkylation product (*R*)-**3** in good yield and moderate enantioselectivity (Scheme 2.1). By switching the catalyst from the cinchonine- to the cinchonidine-derived **4a**, the enantiomer (*S*)-**3** could be obtained with a similar degree of selectivity. One important aspect of this reaction is the selective formation of the monoalkylated product **3**, without concomitant formation of the undesired dialkylated product, as long as the benzophenone Schiff base is employed as a starting substrate [6]. This results from the much lower acidity of the remaining α-proton of **3** compared to that of **1**. This acidity-weakening effect is also crucial for securing the configurational stability of the newly created α-stereogenic center under the reaction conditions. Further optimization with hydroxy-protected catalyst **4b** (second-generation catalyst) enhanced the enantioselectivity to 81% *ee* [7]. A single recrystallization and subsequent acidic hydrolysis of **3** afforded essentially optically pure α-amino acids.

This asymmetric alkylation procedure has been strengthened into an even more practical and valuable protocol through the development of a new class of cinchona alkaloid-derived catalysts bearing an *N*-anthracenylmethyl function (third-generation catalyst). In 1997, Lygo designed *N*-anthracenylmethylammonium salts **2b** and **4c**, and applied them to the asymmetric phase-transfer alkylation of **1** to synthesize α-amino acids with much higher enantioselectivity (Scheme 2.2) [8]. At the same time, Corey prepared *O*-allyl-*N*-anthracenylmethylcinchonidinium salt **4d** and achieved high asymmetric induction by the use of solid $CsOH{\cdot}H_2O$ as a base at very low temperature, as also shown in Scheme 2.2 [9]. The structure of the catalyst was



Scheme 2.2

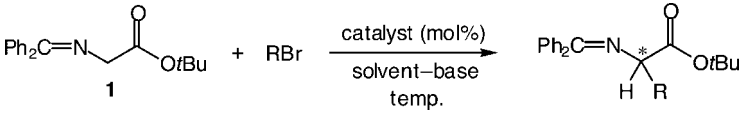
confirmed by X-ray analysis after crystallization of *O*-allyl-*N*-anthracenylmethylcinchonidium *p*-nitrophenoxide.

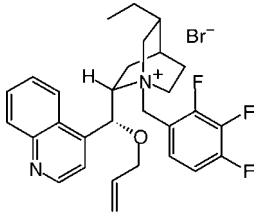
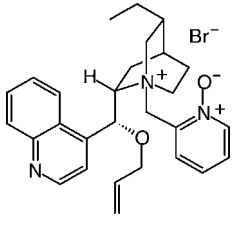
These reports have accelerated research investigations into improving the asymmetric alkylation of **1** in terms of catalytic activity and stereoselectivity, the result being the emergence of a series of appropriately modified cinchona alkaloid-based catalysts. The performance of the representative monomeric catalysts in the asymmetric benzylation and allylation of **1** are summarized in Table 2.1, in order to provide an overview of the relationship between the structure, activity and enantioselectivity.

The phase-transfer-catalyzed asymmetric alkylation of **1** has usually been performed with achiral alkyl halides, and hence the stereochemistry of the reaction with chiral electrophiles has scarcely been addressed. Nevertheless, several groups have tackled this problem. Zhu and coworkers examined the alkylation of **1** with stereochemically defined (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine using **4d** to prepare (2*S*,4*R*)-4-hydroxyornithine for the total synthesis of Biphenomycin. Unexpectedly, however, product **7** with a 2*R* absolute configuration was formed as a major isomer, and the diastereomeric ratio was not affected by switching the catalyst to pseudoenantiomeric **2d** and even to achiral tetrabutylammonium bromide (TBAB), indicating that the asymmetric induction was dictated by the substrate (Scheme 2.3) [21].

Armstrong and Scutt reported a synthesis of 3-(*trans*-2-aminocyclopropyl)alanine, a component of Balactosin A, through the highly diastereoselective alkylation of **1** with optically pure alkyl iodide **8**. Under thoroughly optimized conditions, the

Table 2.1 Cinchona alkaloid-derived monomeric catalysts and their performance in the phase-transfer-catalyzed alkylation of **1**.



Entry	Catalyst (mol.%)	Solvent base, temp.	Yield, *ee* (config.) R = $PhCH_2$ R = $CH_2=CHCH_2$	Reference
1	 **6a** (10)	PhMe/$CHCl_3$ (7 : 3) 50% KOH, −20 °C	96, 98 (*S*) 95, 96 (*S*)	10
2	 **6b** (5)	PhMe/$CHCl_3$ (7 : 3) 50% KOH, −20 °C	93, 98 (*S*) 94, 97 (*S*)	11

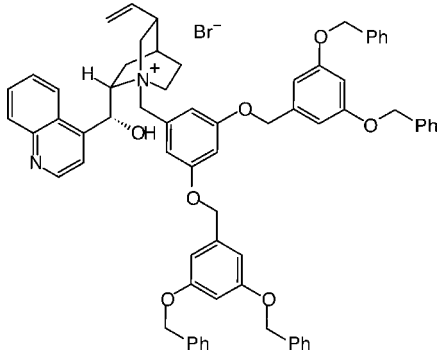
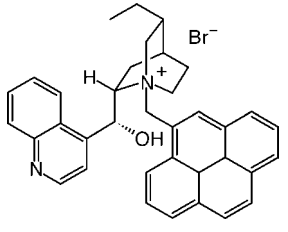
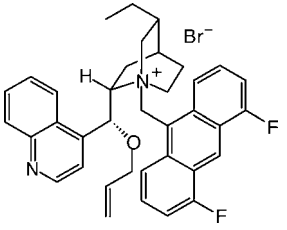
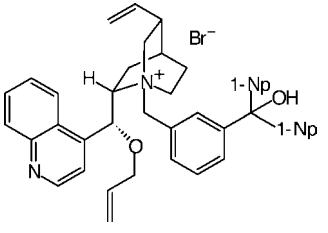
3[a]	 **4e** (10)	PhMe/$CHCl_3$ (7 : 3) 50% KOH, −20 °C	94, 72 (*S*)	12
4	 **6c** (5)	PhMe 50% NaOH, 0 °C	91, 88 (*S*) 94, 89 (*S*)	13

Table 2.1 *(Continued)*

Entry	Catalyst (mol%)	Solvent base, temp.	Yield, *ee* (config.) R=$PhCH_2$ R=CH_2=$CHCH_2$	Reference
5	 **6d** (10)	PhMe/THF (7 : 3) 50% KOH, −40 °C	86, 98 (*S*) 87, 98 (*S*)	14
6	 **4f** (10)	PhMe/CH_2Cl_2 (7 : 3) 50% KOH, −20 °C	93, 92 (*S*) 92, 93 (*S*)	15

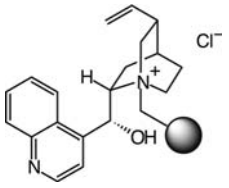
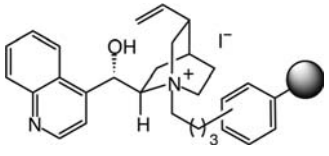
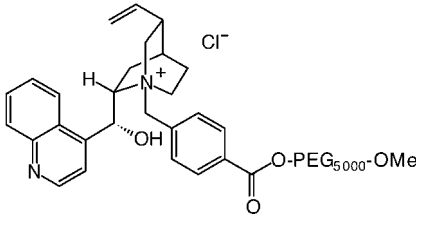
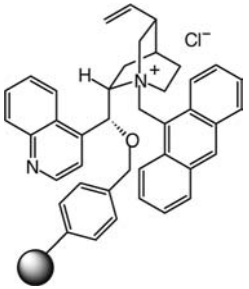
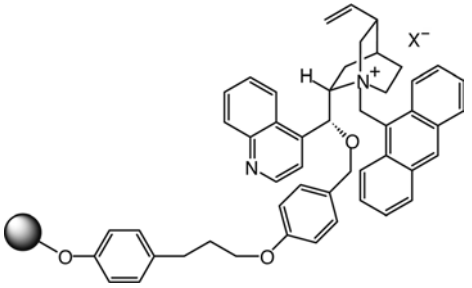
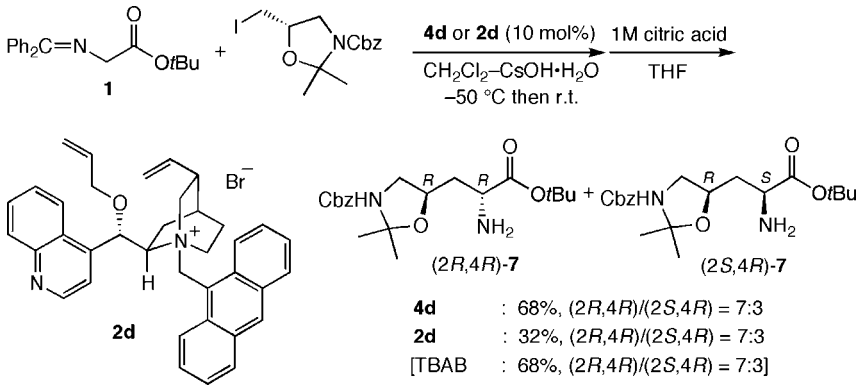
7[a)]	 **4g** (10)	PhMe 25% NaOH, 0 °C	90, 90 (*S*) 75, 32 (*S*)	16
8	 **2c** (10)	PhMe 50% KOH, 0 °C	60, 81 (*R*)	17
9	 **4h** (10)	PhMe 50% KOH, 0 °C	84, 81 (*S*)	18

Table 2.1 *(Continued)*

Entry	Catalyst (mol.%)	Solvent base, temp.	Yield, *ee* (config.) R=$PhCH_2$ R=CH_2=$CHCH_2$	Reference
10	 **4i** (10)	PhMe $CsOH{\cdot}H_2O$, −50 °C	67, 94 (*S*)	19
11	 **4j** (X = CI or Br) (10)	CH_2Cl_2 $CsOH{\cdot}H_2O$, −78 °C	75, 64 (*S*)	20

[a] Isopropyl glycinate benzophenone Schiff base was employed as substrate.

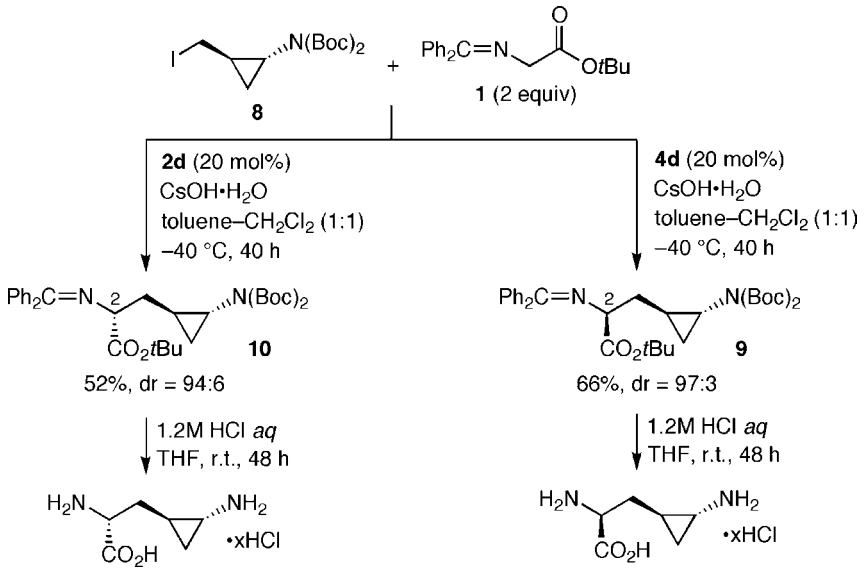


Scheme 2.3

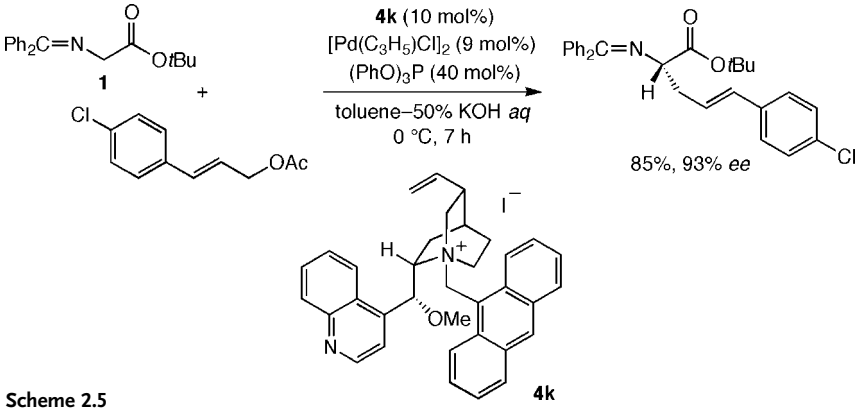
desired products **9** and **10** were obtained in good yields, and the C(2) configuration was rigorously controlled by changing the chirality of the catalyst (Scheme 2.4) [22].

While alkyl halides are typically employed as an electrophile for this transformation, Takemoto developed palladium-catalyzed asymmetric allylic alkylation of **1** using allylic acetates and chiral phase-transfer catalyst **4k**, as depicted in Scheme 2.5 [23]. The choice of triphenyl phosphite [$(PhO)_3P$] as an achiral palladium ligand was crucial to achieve high enantioselectivity.

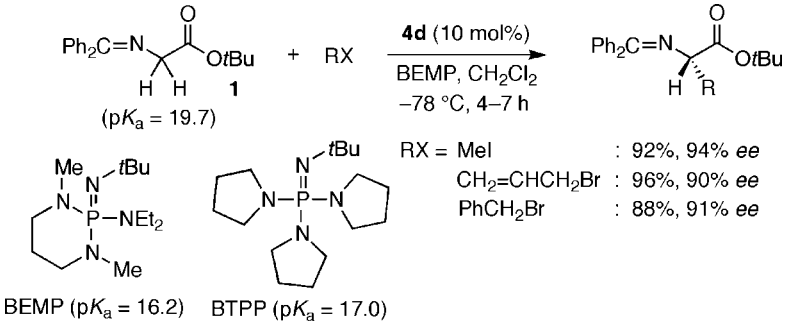
Instead of an aqueous alkaline base, organic-soluble, non-ionic phosphazene bases such as BEMP and BTPP have been used with the third-generation catalyst **4d** to realize a homogeneous system for the asymmetric alkylation of **1** (Scheme 2.6), which is sometimes advantageous from a practical viewpoint [24].



Scheme 2.4



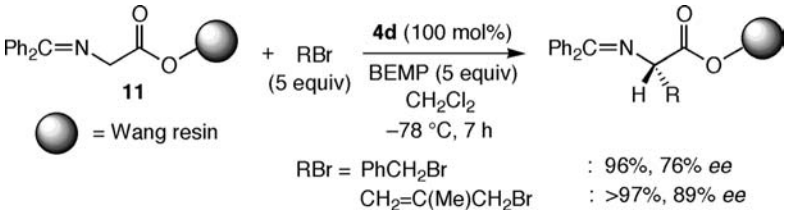
Scheme 2.5



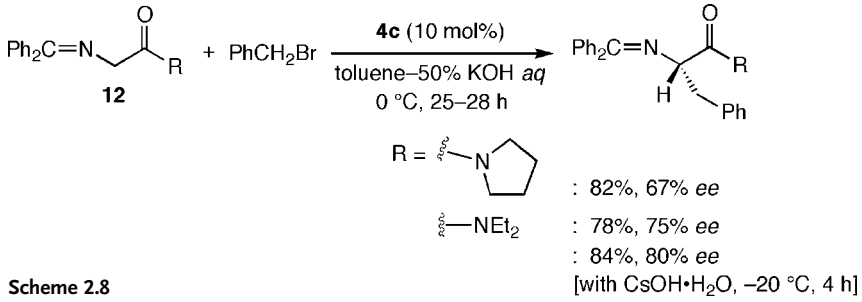
Scheme 2.6

Catalytic asymmetric alkylation of **1** has also been carried out with polymer-bound glycine substrates. For example, O'Donnell and coworkers used Wang resin-bound derivative **11** in combination with BEMP or BTPP and **4d**, as exemplified in Scheme 2.7 [25]. Although a full equivalent of **4d** was required, the promising stereoselectivities provided strong implications for further optimizations.

In addition to the glycinate Schiff base **1**, glycine amide derivatives can be used as prochiral substrates for asymmetric alkylation under phase-transfer conditions. Kumar and Ramachandran examined the benzylation of various Schiff bases of



Scheme 2.7



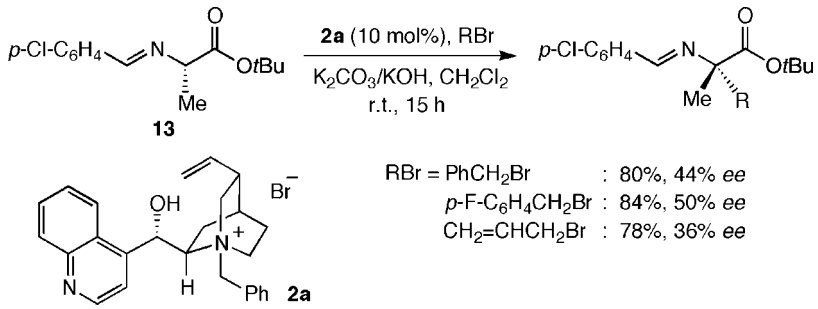
Scheme 2.8

tertiary glycine amides **12**, and demonstrated the effectiveness of cinchonidine-derived **4c** for attaining synthetically satisfactory chemical yields and enantioselectivities (Scheme 2.8) [26].

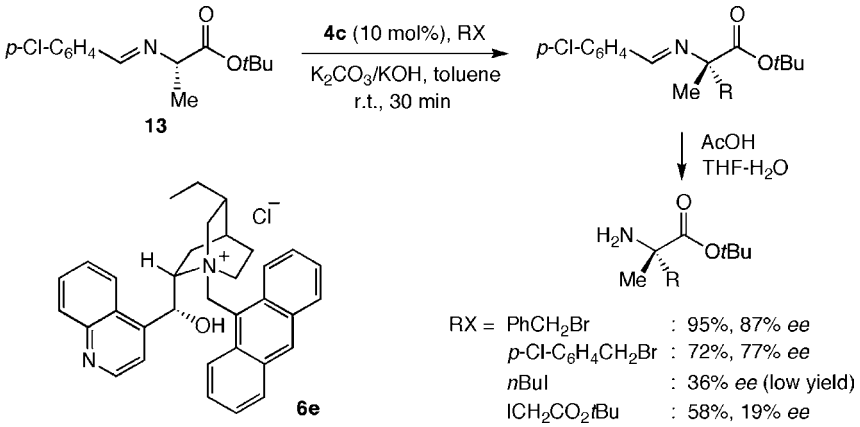
It is also important to note that the potential synthetic utility of the asymmetric alkylation protocol discussed in this section has been fruitfully demonstrated by its application to the stereoselective synthesis of various biologically active natural products possessing unique α-amino acid derivatives as their structural components [27,28].

2.2.2
Alkylation of Schiff Bases Derived from α-Alkyl-α-Amino Acids

Phase-transfer catalysis has made unique contributions in the development of a truly efficient method for the preparation of non-proteinogenic, chiral α,α-dialkyl-α-amino acids, which are often effective enzyme inhibitors and also indispensable for the elucidation of enzymatic mechanisms. In 1992, the group of O'Donnell succeeded in obtaining optically active α-methyl-α-amino acid derivatives in a catalytic manner through the phase-transfer alkylation of *p*-chlorobenzaldehyde imine of alanine *tert*-butyl ester **13** with cinchonine-derived **2a** as catalyst (Scheme 2.9) [29]. Although the enantioselectivities were moderate, this study was the first example of preparing optically active α,α-dialkyl-α-amino acids by chiral phase-transfer catalysis.



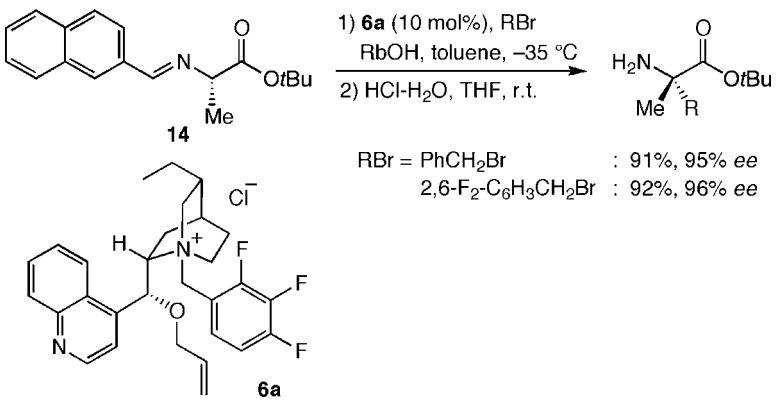
Scheme 2.9



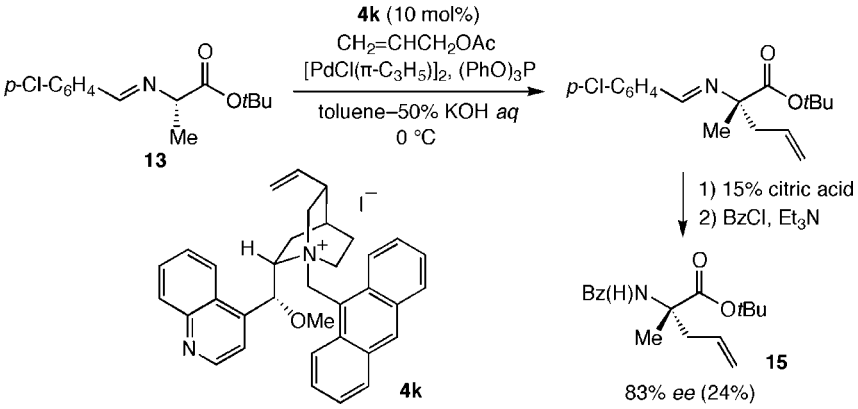
Scheme 2.10

In 1999, the group of Lygo reported that the use of *N*-anthracenylmethyl-dihydrocinchonidinium chloride (**6e**) significantly improved the enantioselectivity of the alkylations with substituted benzyl bromides, enhancing the utility of this approach to α,α-dialkyl-α-amino acids [30]. For reproducible results, the mixed solid base KOH/K_2CO_3 must be freshly prepared before use. The lack of stereoselectivity in the reactions with other electrophiles was ascribed to competing, non-selective background alkylation (Scheme 2.10).

Jew, Park and coworkers performed systematic investigations to develop a more efficient system for the asymmetric synthesis of α-alkylalanines by chiral phase-transfer catalysis [31]. Eventually, sterically more demanding 2-naphthyl aldimine *tert*-butyl ester **14** was identified as a suitable substrate, and its alkylation in the presence of stronger base rubidium hydroxide (RbOH) and *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzyldihydrocinchonidinium bromide (**6a**) at lower reaction temperature led to the highest enantioselectivity (Scheme 2.11).



Scheme 2.11

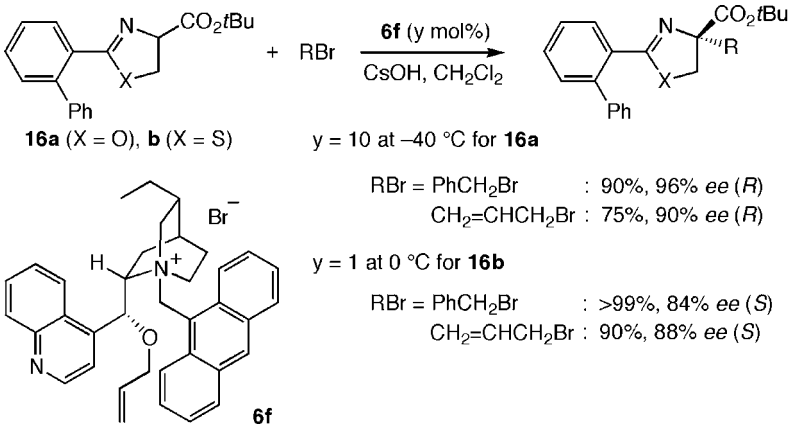


Scheme 2.12

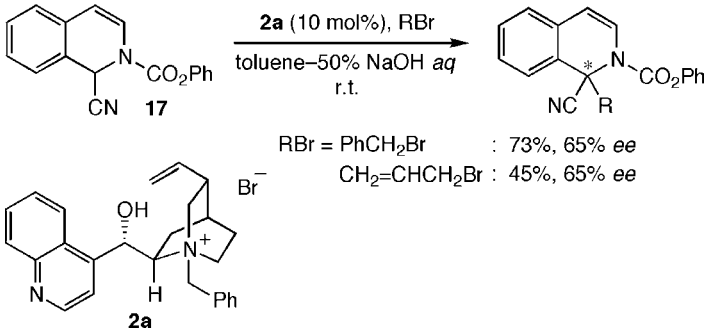
Takemoto and coworkers extended their palladium-catalyzed asymmetric allylic alkylation strategy using allyl acetate and chiral phase-transfer catalyst to the quaternization of **13** [23b]. A correct choice of the achiral palladium ligand, $(PhO)_3P$, was again crucial to achieve high enantioselectivity and hence, without chiral phosphine ligand on palladium, the desired allylation product **15** was obtained with 83% *ee* after hydrolysis of the imine moiety with aqueous citric acid and subsequent benzoylation (Scheme 2.12).

2.2.3
Other Alkylations for α-Amino Acid Synthesis

The group of Jew and Park successfully utilized dihydrocinchonidine-derived **6f** as an efficient catalyst for the asymmetric alkylation of *o*-biphenyl-2-oxazoline- and *o*-biphenyl-2-thiazoline-4-carboxylic acid *tert*-butyl esters (**16a** and **16b**) under mild solid-liquid phase-transfer conditions (Scheme 2.13) [32,33]. These reactions are



Scheme 2.13



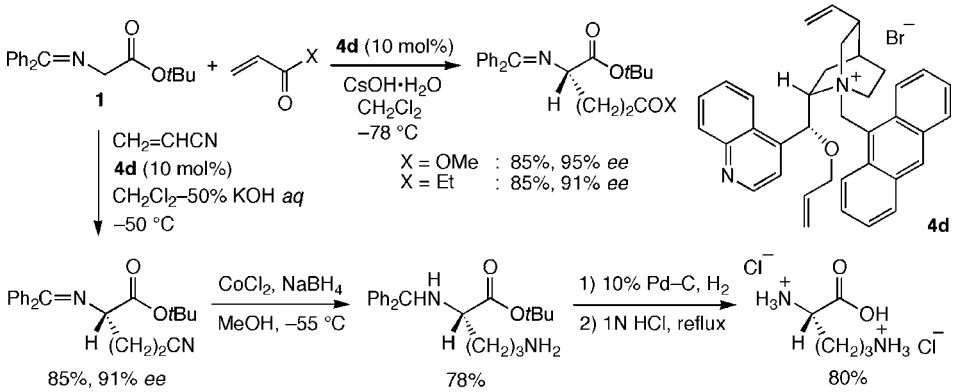
Scheme 2.14

general in nature, and offer practical accesses to a variety of optically active α-alkylserines and α-alkylcysteines through acidic hydrolysis.

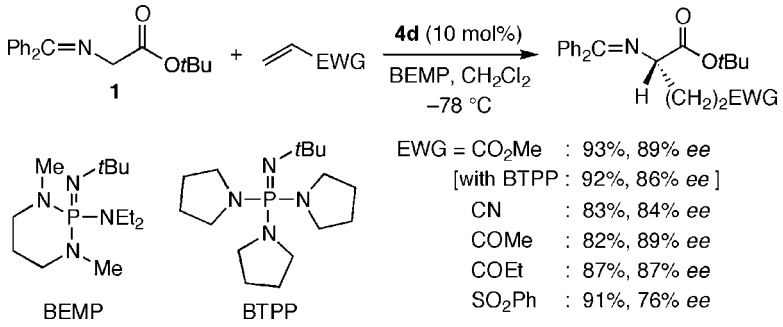
Rozwadowska and coworkers carried out the asymmetric alkylation of isoquinoline Reissert compounds under phase-transfer conditions using cinchonine-derived quaternary ammonium salts as catalysts. The best enantioselectivity was achieved in the benzylation and allylation of 1-cyano-2-phenoxycarbonyl-1,2-dihydroisoquinoline (**17**) catalyzed by **2a** (Scheme 2.14) [34].

2.2.4
Michael Reaction of Glycinate Benzophenone Schiff Bases

Enantioselective Michael addition of glycine derivatives by means of chiral phase-transfer catalysis has been developed to synthesize various functionalized α-alkyl-α-amino acids. Corey utilized **4d** as catalyst for asymmetric Michael addition of glycinate Schiff base **1** to α,β-unsaturated carbonyl substrates with high enantioselectivity (Scheme 2.15) [35,36]. With methyl acrylate as an acceptor, the α-*tert*-butyl-γ-methyl ester of (*S*)-glutamic acid can be produced, a functionalized glutamic acid



Scheme 2.15



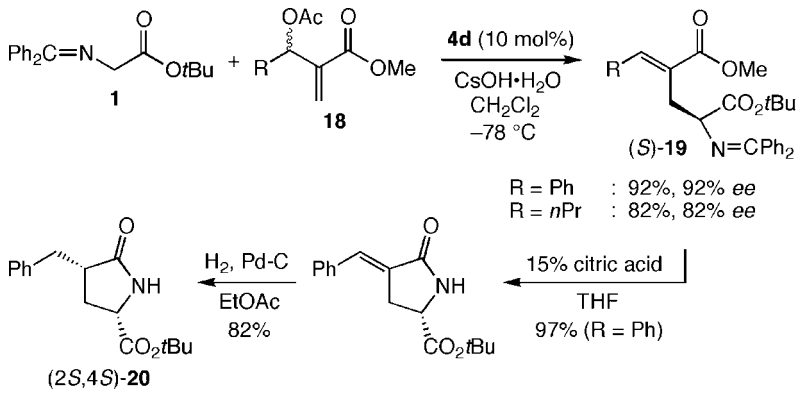
Scheme 2.16

derivative which is very useful for synthetic applications because the two carboxyl groups are differentiated. Moreover, naturally occurring (*S*)-ornithine has been concisely synthesized as its dihydrochloride using acrylonitrile as an acceptor, as also included in Scheme 2.15 [36].

These reliable Michael technologies have been successfully applied to the preparation of all possible ^{13}C and ^{15}N isotopomers of L-lysine, L-ornithine, and L-proline by the group of Lugtenburg [37].

O'Donnell and coworkers conducted this type of Michael addition with the organic-soluble, Schwesinger bases (BEMP and BTPP) (Scheme 2.16). Generally, the less-basic BEMP proved to be superior and tolerated several representative Michael acceptors [38].

An additional interesting example is the conjugate addition of **1** to activated allylic acetates **18** under the chiral phase-transfer catalysis of **4d**, and subsequent elimination reaction, as reported by Ramachandran and coworkers, as this enables the synthesis of various enantiomerically enriched glutamic acid derivatives [39]. The utility of this process has been demonstrated by the transformation of (*S*)-**19** (R = Ph) into 4-substituted pyroglutamate (2*S*,4*S*)-**20**, as illustrated in Scheme 2.17.

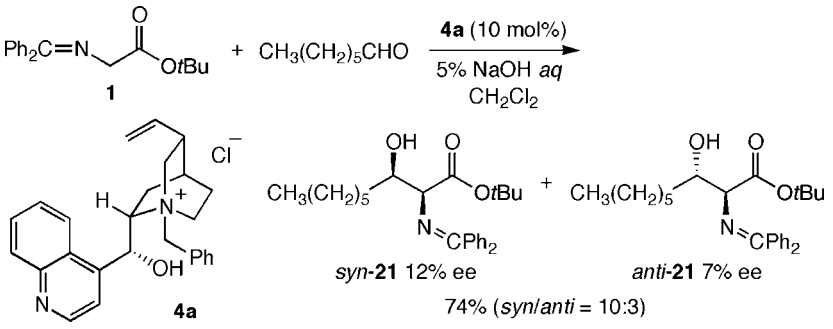


Scheme 2.17

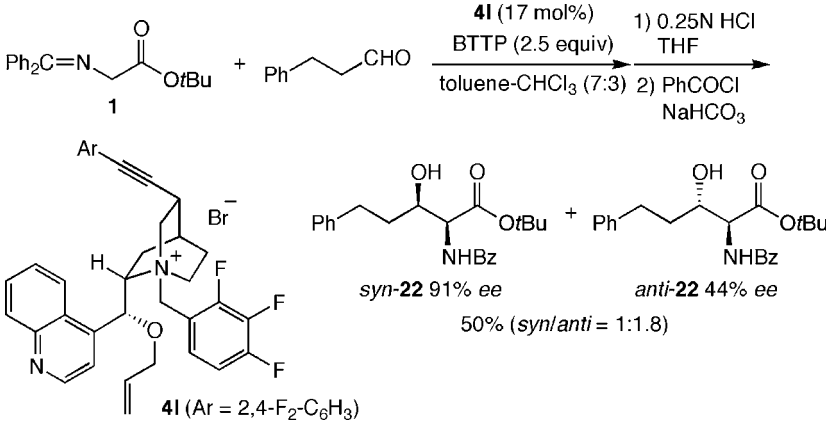
2.2.5
Aldol and Related Reactions

The phase-transfer-catalyzed enantioselective direct aldol reactions of glycine donor with aldehyde acceptors provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids, which are extremely important chiral units. In the first report from the Miller's group, *N*-benzylcinchonidinium chloride (**4a**) was employed as a catalyst for the reaction of **1** with heptanal, and the corresponding aldol product **21** was obtained in 74% yield, though the diastereo- and enantioselectivities were unfortunately not satisfactory (Scheme 2.18) [40].

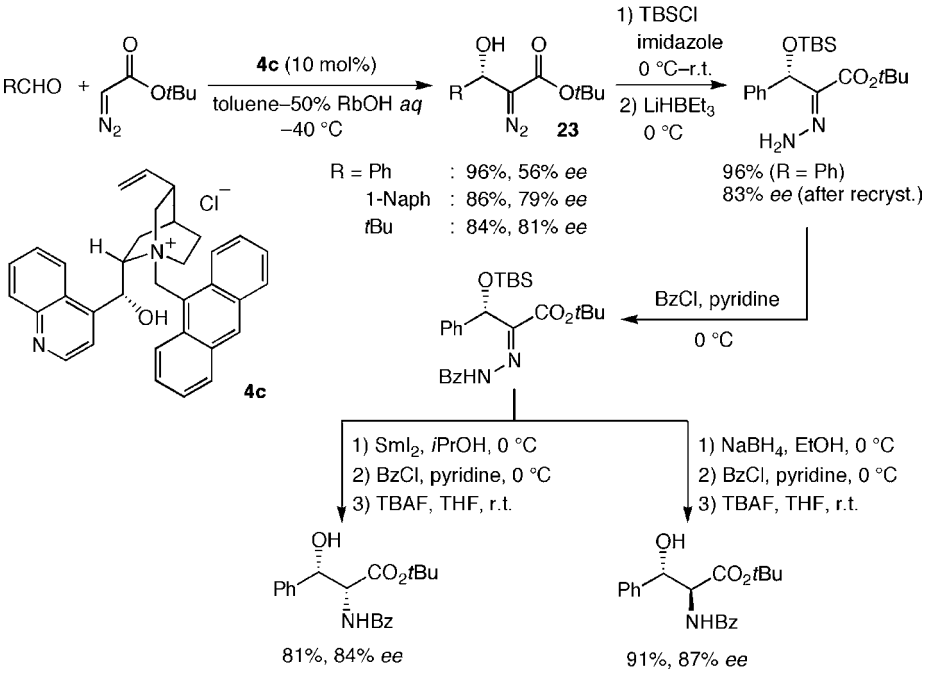
Recently, Castle and coworkers introduced C3-alkynyl-substituted chiral quaternary ammonium salt of type **4l**, and evaluated its ability as a chiral phase-transfer catalyst in the aldol reaction between **1** and hydrocinnamaldehyde using BTTP as a base, in which a high level of enantioselectivity (91% ee) was observed for *syn*-**22** (Scheme 2.19) [41].



Scheme 2.18



Scheme 2.19

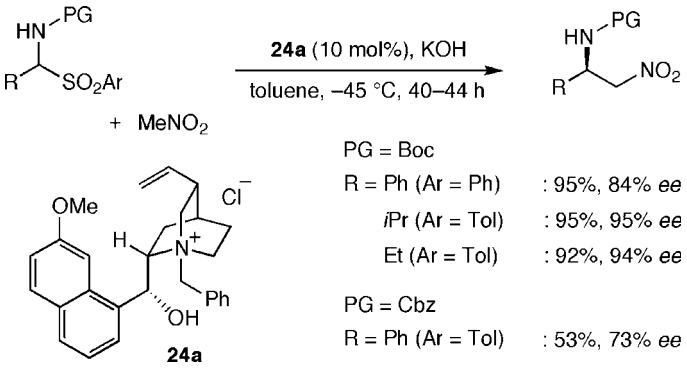


Scheme 2.20

The group of Arai and Nishida investigated the catalytic asymmetric aldol reaction between *tert*-butyl diazoacetate and various aldehydes under phase-transfer conditions with chiral quaternary ammonium chloride **4c** as a catalyst. The reactions were found to proceed smoothly in toluene, even at −40 °C, when using 50% RbOH aqueous solution as a base, giving rise to the desired aldol adducts **23** with good enantioselectivities. The resulting **23** can be stereoselectively transformed into the corresponding *syn*- or *anti*-β-hydroxy-α-amino acid derivatives (Scheme 2.20) [42].

2.2.6
Aza-Henry Reaction

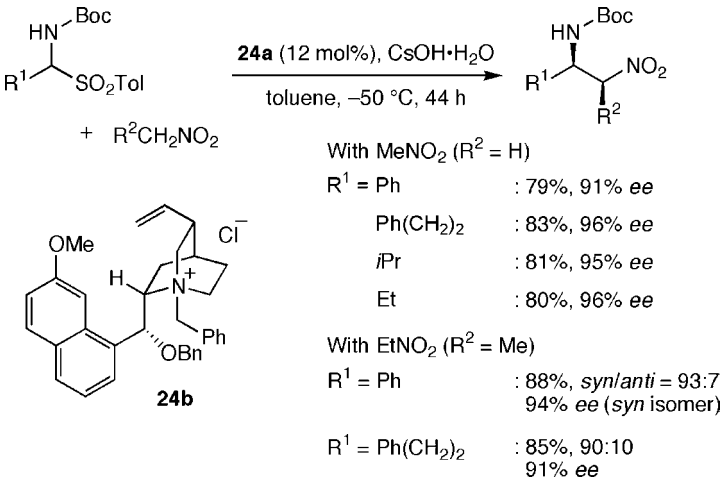
The catalytic asymmetric variants of aza-Henry reaction have attracted a great deal of attention in recent years, partly because the resulting β-nitro amines can be readily derivatized into highly valuable chiral building blocks such as α-amino acids and vicinal diamines. In late 2005, two research groups independently reported the catalytic asymmetric addition of nitroalkanes to *N*-alkoxycarbonyl imines generated *in situ* from α-amido sulfones with cinchona alkaloid-derived quaternary ammonium slats as catalysts by nicely taking advantage of the biphasic conditions. First, Herrera, Bernardi, Ricci and coworkers showed that the addition of nitromethane to a wide range of *in-situ*-generated aromatic and aliphatic *N*-*tert*-butoxycarbonyl (Boc) imines



Scheme 2.21

proceeded with high enantioselectivity under solid-liquid phase-transfer conditions by the use of quinine-derived **24a** as a catalyst and powdered KOH as a base. Although the benzyloxycarbonyl (Cbz) group can also be employed for the nitrogen protection, a certain decrease in enantioselectivity was observed (Scheme 2.21) [43].

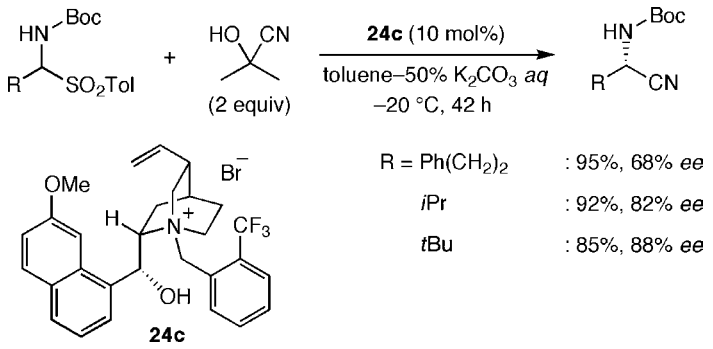
In contrast, Palomo and coworkers emphasized the effectiveness of using $CsOH{\cdot}H_2O$ as a solid base in combination with the catalyst **24a**. Moreover, they investigated the reactions of nitroethane with various *N*-Boc imines, in which the *syn*-adduct was obtained predominantly, with a high degree of enantioselectivity (Scheme 2.22) [44]. It was of interest that catalyst **24b**, the hydroxy group of which was protected in the form of a benzyl ether, displayed significantly lower efficiency (typically <10% conversion). This suggested that a hydrogen-bonding interaction between the free hydroxyl group and the nitro group's oxygen or the azomethine's nitrogen would play a key role in this highly stereoselective transformation.



Scheme 2.22

2.2.7
Strecker Reaction

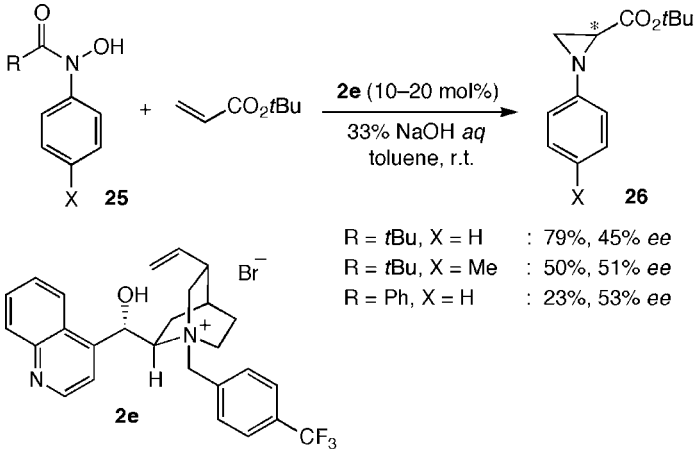
The catalytic asymmetric Strecker reaction represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. Although a number of highly efficient and truly general protocols have thus been established to provide a reliable access to a wide range of optically active α-amino nitriles, the majority of the previously elaborated catalytic asymmetric Strecker methodologies rely on the use of either alkylmetal cyanide or anhydrous hydrogen cyanide, generally at low temperature. The asymmetric cyanation of imines under mild phase-transfer conditions using readily available, easy-to-handle cyanide sources could provide a unique solution to this problem. For example, the group of Herrera, Bernardi and Ricci realized the enantioselective synthesis of protected α-amino nitriles from the corresponding α-amido sulfones under biphasic conditions by the use of acetone cyanohydrin as a cyanide source in the presence of an excess amount of aqueous base and quinine-derived catalyst **24c** (Scheme 2.23) [45].



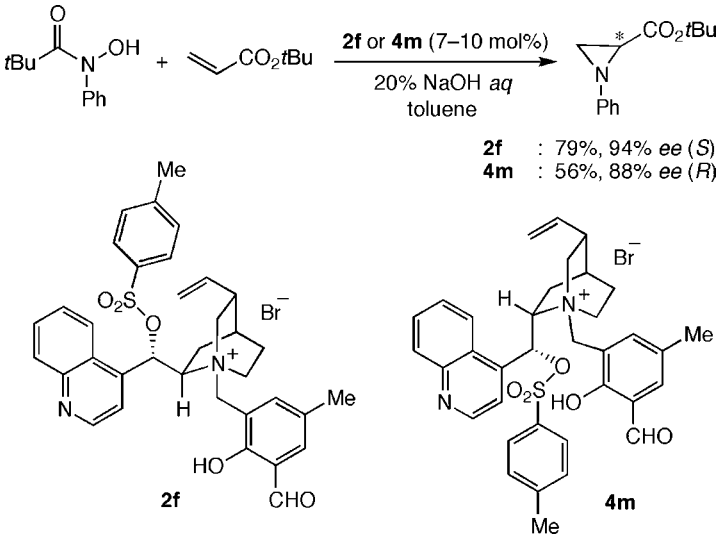
Scheme 2.23

2.2.8
Aziridination

The asymmetric aziridination of α,β-unsaturated carboxylic acid derivatives is a direct route to optically active aza-cyclic α-amino acids, and this class of chiral aziridines can also be used as chiral building blocks for the preparation of other amino acids, β-lactams, and alkaloids. Prabhakar and coworkers carried out an asymmetric aziridination reaction of *tert*-butyl acrylate with *O*-pivaloyl-*N*-arylhydroxylamine **25** in the presence of cinchonine-derived chiral ammonium salt **2e** under phase-transfer conditions, which furnished the corresponding chiral *N*-arylaziridine **26** with moderate enantioselectivity (Scheme 2.24) [46].



Scheme 2.24

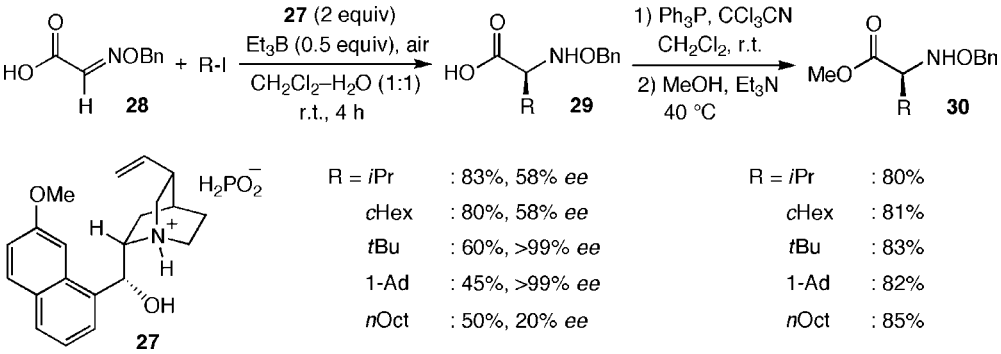


Scheme 2.25

Murugan and Siva developed a new procedure for such asymmetric aziridination reactions to achieve an excellent level of enantioselectivity using new chiral phase-transfer catalysts **2f** and **4m** derived from cinchonidine and cinchonine, respectively (Scheme 2.25) [47].

2.2.9
Radical Reaction

In the situation that the chiral phase-transfer catalysis has scarcely been applied for the radical reaction, Jang and Cho recently developed the enantioselective addition of



Scheme 2.26

alkyl radicals to glyoxylate oxime ether **28** under biphasic conditions, based on the use of chiral quaternary ammonium hypophosphite **27** as a mediator and Et_3B/O_2 as an initiator. The reaction of **28** with secondary alkyl iodides proceeded smoothly to afford **29** with moderate enantioselectivity, which was determined after conversion into its methyl ester **30**. Notably, virtually complete stereochemical control was achieved in the reactions with tertiary alkyl iodides, as shown in Scheme 2.26 [48].

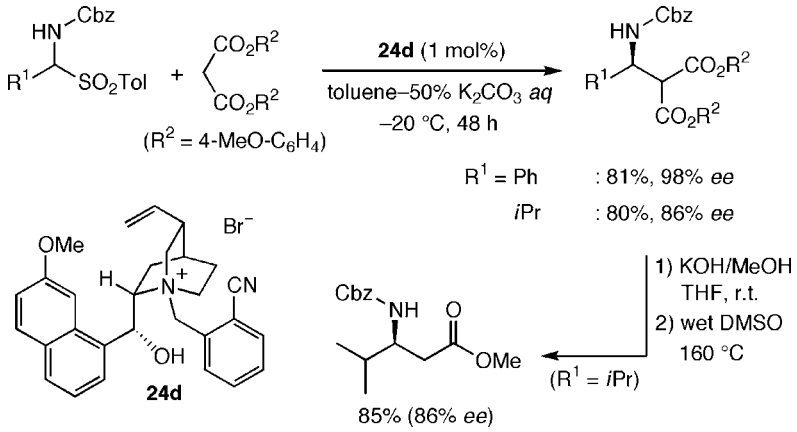
2.3
β-Amino Acid Synthesis

2.3.1
Mannich Reaction

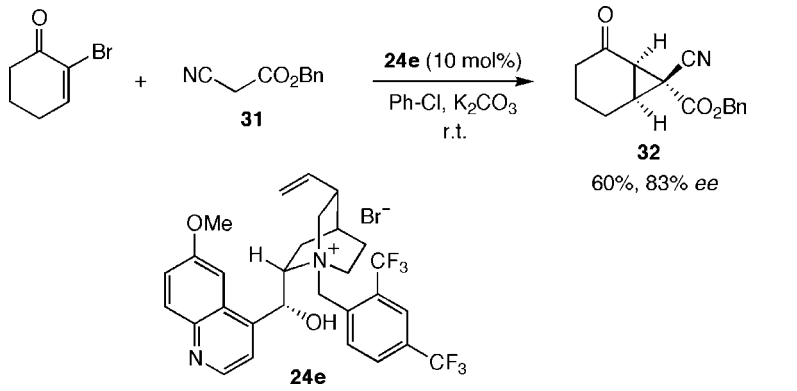
The research group of Herrera, Bernardi and Ricci extended the strategy of generating the reactive *N*-Boc or *N*-Cbz imines *in situ* by exploiting phase-transfer-catalyzed conditions to the asymmetric direct Mannich reaction of malonates, thus providing a practical access to various optically active β-amino acids and their derivatives. Optimization of the reaction parameters, including the catalyst structure, revealed that the use of 1 mol% of **24d** was sufficient to facilitate the highly enantioselective addition of *p*-anisyl malonate to the *in-situ*-generated *N*-Cbz imines in toluene: 50% K_2CO_3 at −20 °C. The resulting Mannich adduct could be readily converted into the corresponding protected β-amino acid through a decarboxylation-transesterification sequence without loss of the enantiomeric excess (*ee*), as included in Scheme 2.27 [49].

2.3.2
Cyclopropanation

The asymmetric cyclopropanation of α-bromocyclohexenone with cyanoacetate **31** has been achieved under phase-transfer conditions by the use of cinchona alkaloid-derived catalyst, which constructs chiral quaternary carbons on the cyclopropane



Scheme 2.27



Scheme 2.28

rings, while the products serve as a precursor of highly functionalized β-amino acid derivatives. An extensive survey of the structure of quinine-based ammonium bromide, as well as the reaction conditions, revealed that the desired product **32** was obtained in 60% yield with 83% *ee* by performing the reaction in chlorobenzene at room temperature in the presence of **24e** having an electron-deficient 2,4-bis (trifluoromethyl)-phenylmethyl group and K_2CO_3 (Scheme 2.28) [50].

2.4 Conclusions

As reviewed in this chapter, cinchona alkaloids have played a crucial role in the development of asymmetric phase-transfer catalysis since its advent, and today constitute a privileged structural motif that may be widely utilized for the design of new chiral quaternary ammonium salts. These benefits are due not only to the

availability of different forms of the two pseudoenantiomers, but also to the unique structural features of the chiral scaffold provided by the *N*-alkylated salts. Whilst appreciating that the full potential of asymmetric phase-transfer catalysis is yet to be realized in terms of reactivity, selectivity and general applicability, conceptual advances in catalyst design by harnessing the advantages of cinchona alkaloids as a basic chiral unit are essential in this field. One promising direction to take might be to develop multi-functional, chiral phase-transfer catalysts through the appropriate introduction of other acidic or basic functionalities into the parent alkaloids and/or nitrogen alkylating agents. These should be of major benefit in creating a diverse array of chemical transformations that may be catalyzed in a truly sustainable and highly stereoselective manner.

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3
Cinchona-Derived Chiral Phase-Transfer Catalysts for Other Asymmetric Synthesis

Shigeru Arai

3.1
Introduction

Phase-transfer catalysis has been recognized as one of the most powerful synthetic tools for establishing practical protocols because it offers several advantages, such as operational simplicity, mild conditions with aqueous media, suitability for large-scale reaction, and an environmentally benign nature. Since the pioneering studies on asymmetric alkylation promoted by chiral phase-transfer catalysts (PTCs) [1,2], this research area has served as an attractive area for the pursuit of "green chemistry", and many types of chiral quaternary ammonium salts for various asymmetric phase-transfer catalyses have been developed over the past few decades [3,4]. For example, two-center organocatalysis using bis-ammonium salts derived from tartrate represents a new concept in asymmetric PTC chemistry [5].

In particular, it is not only the cinchona alkaloids that are suitable chiral sources for asymmetric organocatalysis [6], but also the corresponding ammonium salts. Indeed, the latter are particularly useful for chiral PTCs because: (1) both pseudo enantiomers of the starting amines are inexpensive and available commercially; (2) various quaternary ammonium salts can be easily prepared by the use of alkyl halides in a single step; and (3) the olefin and hydroxyl functions are beneficial for further modification of the catalyst. In this chapter, the details of recent progress on asymmetric phase-transfer catalysis are described, with special focus on cinchona-derived ammonium salts, except for asymmetric alkylation in α-amino acid synthesis.

3.2
Asymmetric Darzens Reaction

The Darzens reaction is a fundamental reaction, the products of which are extremely useful for the synthesis of other molecules. Despite these advantages, the reaction

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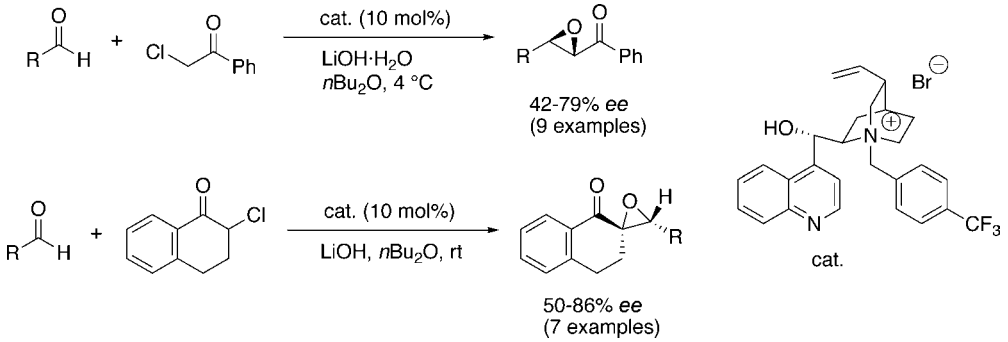


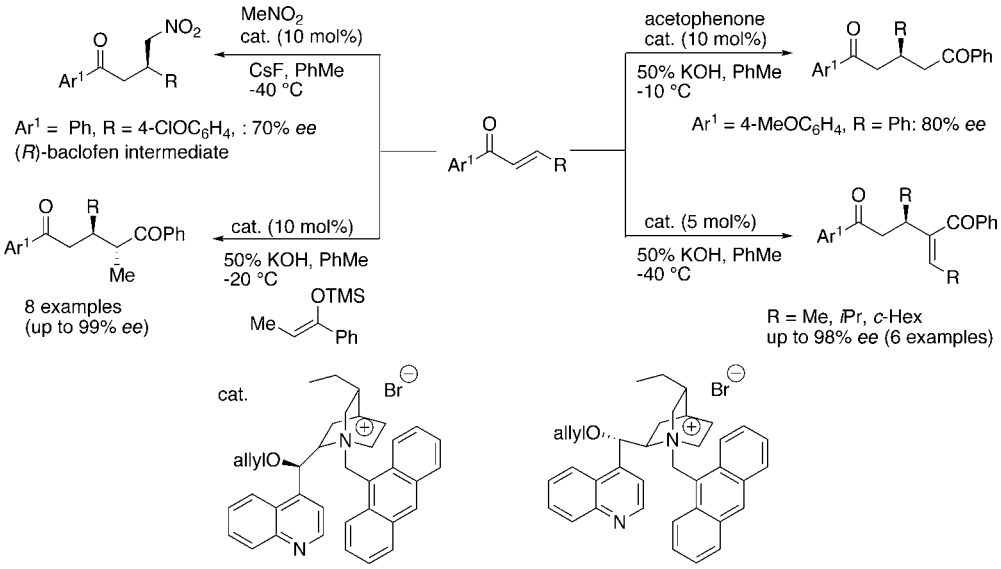
Scheme 3.1 Asymmetric Darzens reaction using chloroketones.

has not been applied to catalytic asymmetric for several reasons: (1) a stoichiometric amount of base is converted to the corresponding metal halide (MX) (*not reusable*); and therefore (2) a catalytic cycle with chiral metal-base catalysts cannot be proposed. On the other hand, it is well known that acidic organic molecules with quaternary ammonium halides (QX) and inorganic base produce ammonium anions (nucleophiles), which react with aldehydes to give Darzens products, together with QX. This proposal makes it possible to establish a catalytic cycle in the asymmetric Darzens reaction under phase-transfer catalysis, as described by Shioiri and Arai. These authors described a reaction using cyclic and acyclic α-chloroketones with aldehydes in the presence of chiral PTC to give optically active epoxyketones (Scheme 3.1) [7–9]. The diastereoselectivity is controlled to be exclusively *trans*: this indicates that an α-hydrogen of the aldol intermediates can be easily epimerized to the favored conformation for epoxide formation. α-Chlorosulfone [10,11] and amides [12] can also be used in similar manner.

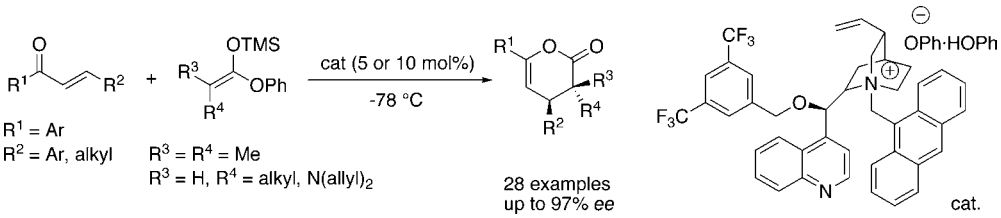
3.3
Asymmetric Conjugated Addition

Since Corey's group first reported *O*(9)-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide as a new phase-transfer catalyst [13], its application to various asymmetric reactions has been investigated. In particular, this catalyst represents a powerful tool in various conjugated additions using chalcone derivatives (Scheme 3.2). For example, nitromethane [14], acetophenone [15], and silyl enolates [16] produce the corresponding adducts in high enantioselectivity. When β-alkyl substrates are used under PTC conditions, asymmetric dimerization triggered by the abstraction of a γ-proton proceeds smoothly. with up to 98% *ee* [17].

Silyl enolates are useful carbon nucleophiles in the asymmetric tandem Michael addition and lactonization (Scheme 3.3). Mukaiyama recently reported that cinchona-derived ammonium phenoxides act as activators (nucleophilic catalysis), to give highly stereocontrolled products [18–20]. In a typical PTC manner, most of the



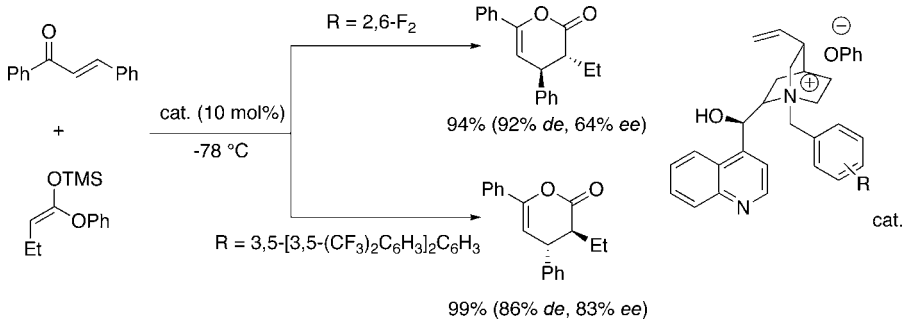
Scheme 3.2 Asymmetric conjugated addition using various carbon nucleophiles.



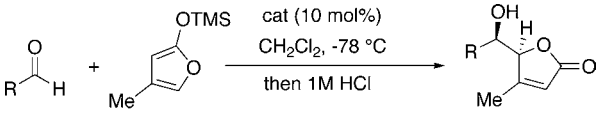
Scheme 3.3 Tandem Michael addition and lactonization using chiral ammonium phenoxide.

counter anions in chiral ammonium catalysts are halides: for example, fluoride anion itself acts as a base, while chloride and bromide are converted to other anionic species under basic media. Mukaiyama's organonucleophilic catalyst provides a new aspect of cinchona-derived ammonium salts in asymmetric catalysis. Hydroxy-free ammonium phenoxides are useful catalysts for preparing both enantiomers from a single catalyst source [21]. Aryl functionalities such as 2,6-$F_2C_6H_3$ and 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$ play a significant role in enantioselection, and give the corresponding *anti*-adducts with respective enantiomeric excess (ee)-values of 64% and 83% (Scheme 3.4). They can also be used in the asymmetric synthesis of butenolides (Scheme 3.5) [22]. The reaction of siloxyfurans with various aldehydes yielded predominantly the *syn*-adducts, with up to 97% *ee*.

α-Pentyl cyclopentenone is a useful Michael acceptor for the synthesis of (+)-methyl jasmonate. The use of dimethylmalonate under PTC conditions gave a key



Scheme 3.4 Catalyst-controlled synthesis of 3,4-dihydropyran-2-ones.

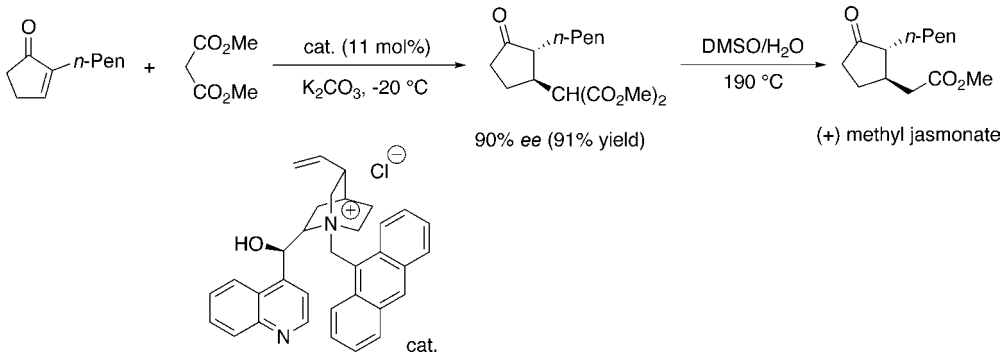


R = aromatic, aliphatic (8 examples)
41-97% yield (57-97% *ee* for *syn*-isomer)
syn:*anti*: up to >99:1

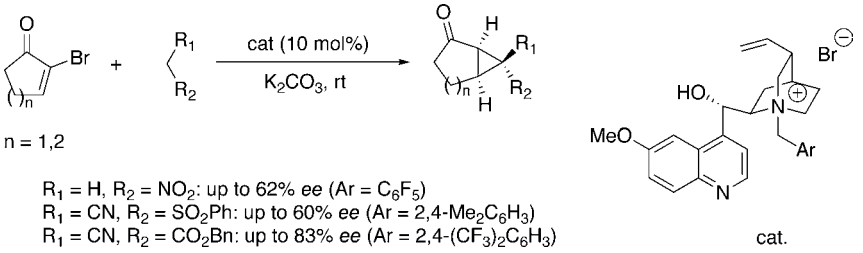
Scheme 3.5 Asymmetric synthesis of butenolides.

intermediate with 90% *ee* (Scheme 3.6). This protocol enables the facile preparation of both enantiomers by changing the catalyst [23].

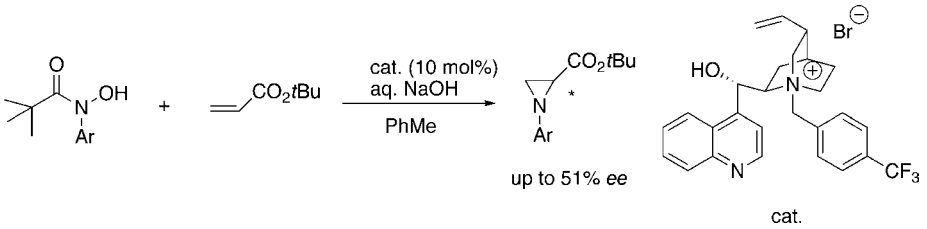
α-Bromocycloalkenones react with Michael donors, and subsequent proton-transfer and cyclization produces stereocontrolled cyclopropanes (Scheme 3.7). This asymmetric protocol allows the use of various substrates such as nitromethane, cyanosulfone and cyanoester to achieve up to 83% *ee* [24]. *N*-Aryhydroxamates act as nitrogen-transfer reagents to give *N*-arylaziridines via conjugated addition. The reaction with acrylate produces optically active aziridines, with 51% *ee* (Scheme 3.8) [25].



Scheme 3.6 Asymmetric Michael addition of malonate.



Scheme 3.7 Asymmetric cyclopropanation of cycloalkenones.

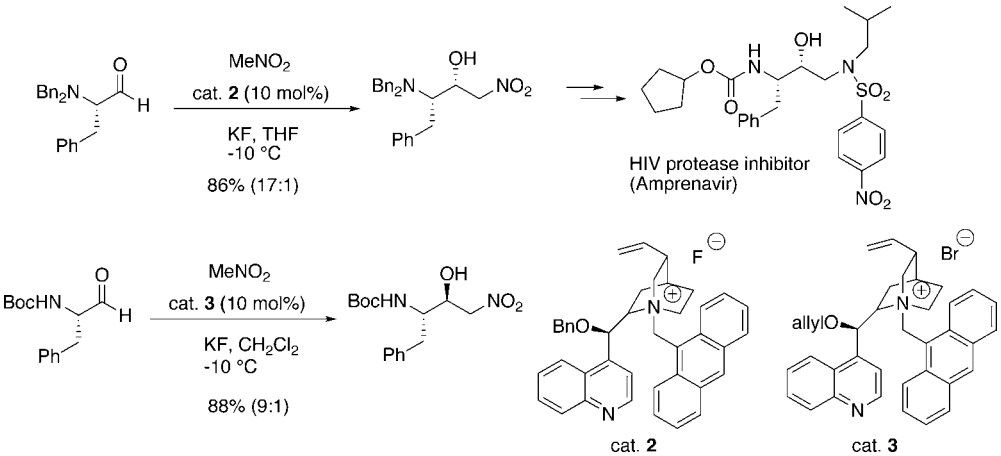


Scheme 3.8 Asymmetric aziridination of acrylate.

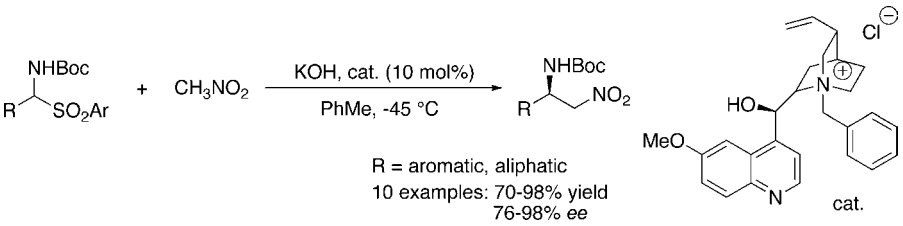
3.4
Asymmetric Aldol Reaction

Corey and colleagues applied their catalyst to the asymmetric Henry (nitro aldol) reaction using chiral aminoaldehydes and the short-step synthesis of an HIV protease inhibitor (Scheme 3.9) [26]. Interestingly, a newly generated asymmetric center is controlled by the chiral catalyst and nitrogen substituents.

α-Amido sulfones are suitable for imine precursors, and an asymmetric aza-Henry reaction using nitromethane has been established (Scheme 3.10) [27]. A wide range



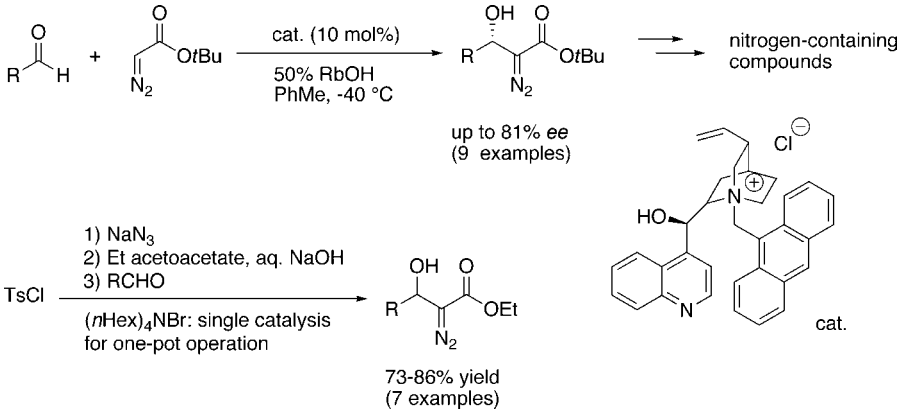
Scheme 3.9 *re*- and *si*-Face-selective Henry reaction.



Scheme 3.10 Asymmetric aza-Henry reaction.

of substrates (R = aromatic, heteroaromatic, primary and secondary aliphatic systems) can be used in the range of 73 to 98% *ee*.

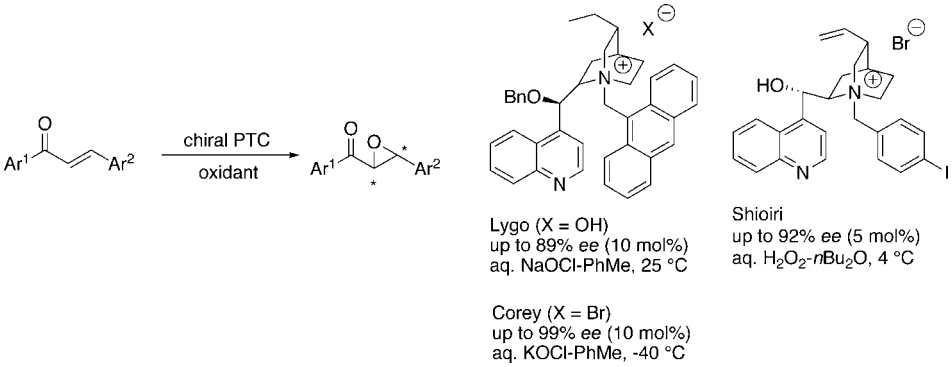
α-Diazoacetates are easily converted into carbanion species in the presence of inorganic bases to react with electrophiles. Nishida and Arai reported that PTC conditions with diazoacetate and various aldehydes gave the corresponding adducts with up to 81% *ee*. A simple operation through a single phase-transfer catalysis starting from TsCl, without any isolation of explosive intermediates, has also been established (Scheme 3.11) [28]. These products are versatile intermediates for nitrogen-containing, biologically important molecules [29].



Scheme 3.11 Asymmetric diazo-aldol reaction and one-pot synthesis.

3.5
Asymmetric Oxygen-Functionalization

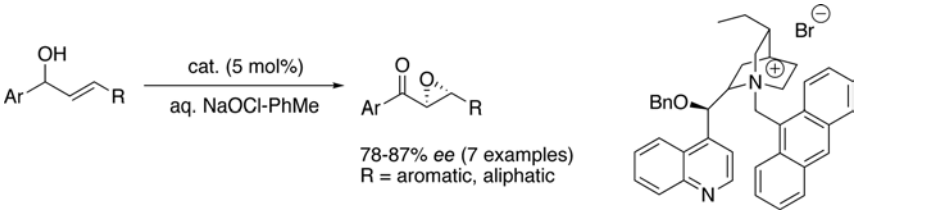
The catalytic asymmetric epoxidation of electron-deficient olefins has been regarded as one of the most representative asymmetric PTC reactions, and various such systems have been reported (Scheme 3.12). Lygo reported the asymmetric epoxidation of chalcone derivatives through the use of NaOCl [30,31], while Shioiri and Arai used aqueous H_2O_2 as an oxidant, their results indicating hydrogen bonding between the catalyst and substrates because an OH functionality in the catalyst was essential



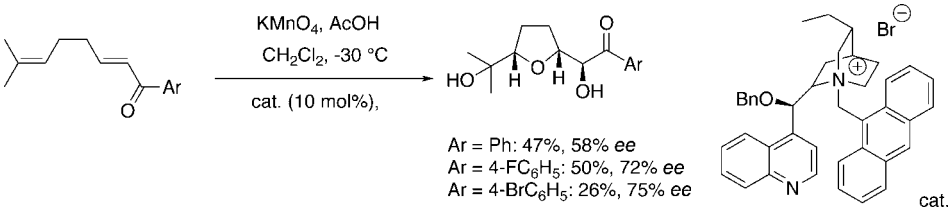
Scheme 3.12 Asymmetric epoxidation of chalcone derivatives.

[33]. Corey *et al.* achieved over 90% *ee* by using their catalyst with KOCl at –40 °C [33]. Allylic alcohols can be used in the above asymmetric reaction through direct conversion to chiral epoxyketones with aromatic and aliphatic side chains (Scheme 3.13) [34].

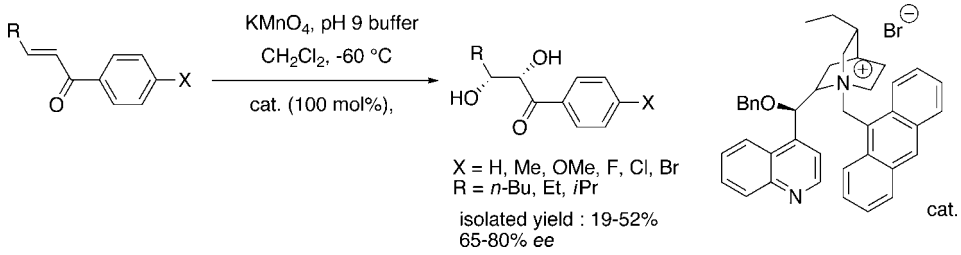
Permanganese is a common oxidative reagent, the application of which to the asymmetric oxidative cyclization of 1,5-dienes has been reported by Brown (Scheme 3.14). The addition of acetic acid is quite important for the reaction to proceed, and highly functionalized tetrahydrofurans are obtained in a range of 58 to 75% *ee*, in diastereoselective manner [35]. Another oxidative transformation using $KMnO_4$ with a chiral ammonium salt has been investigated. Scheme 3.15 illustrates the asymmetric dihydroxylation of electron-deficient olefins to chiral diols in the



Scheme 3.13 Direct conversion of allylic alcohols to epoxyketones.



Scheme 3.14 Asymmetric oxidative cyclization of 1,5-dienes.



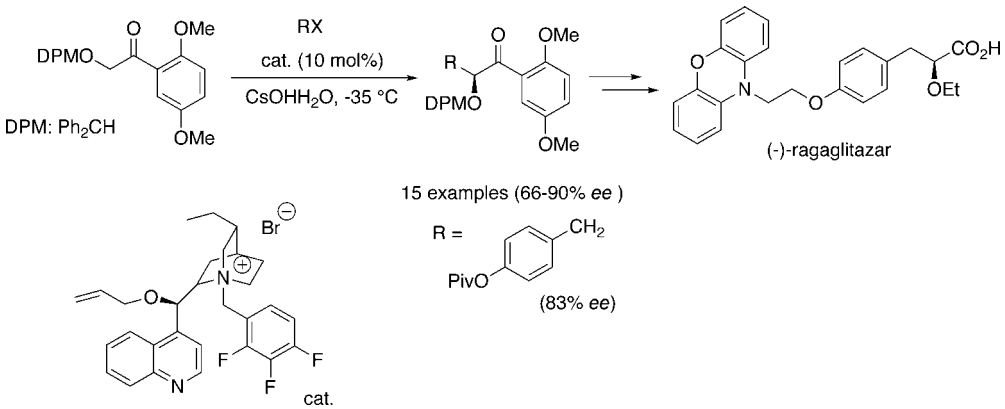
Scheme 3.15 PTC-promoted asymmetric dihydroxylation using $KMnO_4$.

presence of buffer (pH 9). This protocol requires the use of a stoichiometric amount of chiral ammonium salt (*non-catalytic*) [36].

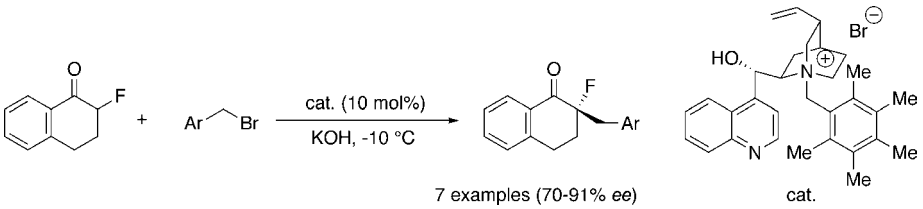
3.6 Asymmetric Alkylation

The asymmetric α-alkylation of carbonyl compounds is a fundamental reaction. Under PTC conditions, acidic substrates such as phenylketone derivatives can be used to create chiral stereogenic centers. Andrus demonstrated asymmetric glycolate alkylation with up to 90% *ee* using various electrophiles and its application to the synthesis of (–)-ragaglitazar in six steps (Scheme 3.16) [37–39].

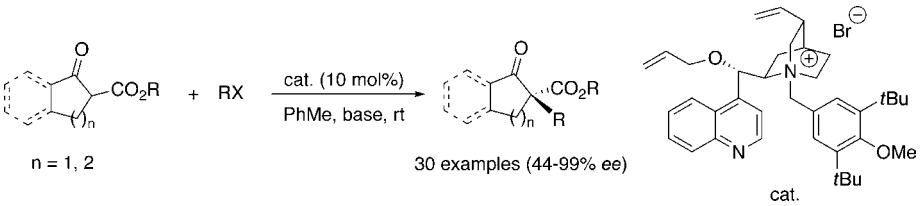
α-Fluorotetralone, which is a more acidic substrate, is suitable for use in asymmetric benzylation under mild conditions (Scheme 3.17). Enantioselectivity is strongly influenced by an aromatic moiety of the catalyst, and a pentamethyl derivative was the catalyst of choice to achieve 91% *ee* [40]. The asymmetric alkylation of cyclic β-ketoesters with various allyl and benzyl halides under PTC conditions has been reported by Kim (Scheme 3.18). In particular, this reaction system is quite efficient when *p*-nitrobenzyl bromide is used as an electrophile (99% *ee*) [41].



Scheme 3.16 Asymmetric alkylation of glycolate.



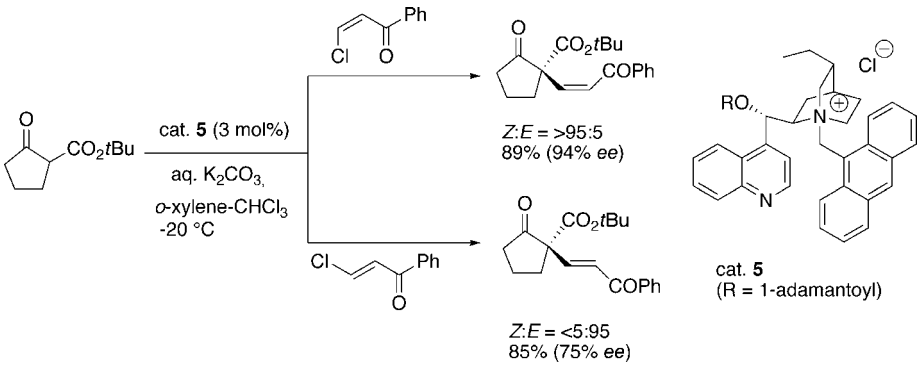
Scheme 3.17 Asymmetric benzylation of fluorotetralone.



Scheme 3.18 Asymmetric alkylation of β-ketoesters.

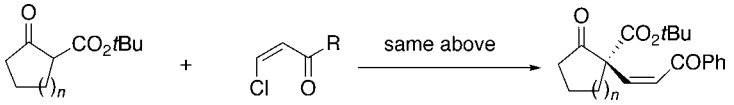
3.7
Asymmetric Alkenylation and Alkynylation

Very recently, Jørgensen reported the asymmetric alkenylation of β-ketoesters using β-chloroenones (vinyl substitution) [42]. This process gives highly stereocontrolled products with regards to both enantioselectivity and diastereoselectivity, with high chemical yields. The diastereoselectivity of the products depends on the starting alkenes; for example, *E*- and *Z*-chloroenones give the corresponding adducts with up to >95 : 5 with broad substrate generality (Scheme 3.19 and Table 3.1). A trisubstituted alkene and tetralone and indanone of 2-carboxylates can also be used in similar



Scheme 3.19 Asymmetric alkenylation using (*Z*)- and (*E*)-β-chloroenones.

Table 3.1 Various substrates in asymmetric alkenylation.

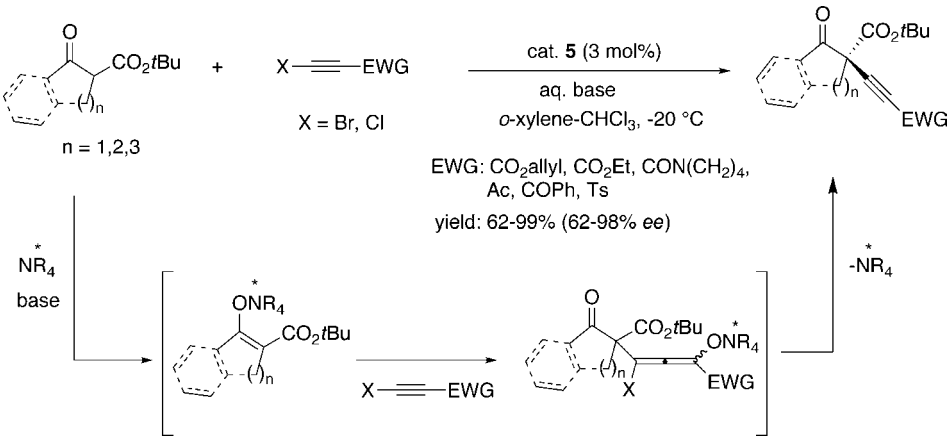


Entry	*n*	R	Yield (%)	*Z*/*E*	*ee* (%)[a]
1	1	4-$CF_3C_6H_4$	89	>95 : 5	93
2	1	4-$MeOC_6H_4$	71	>95 : 5	93
3	1	2-thienyl	87	>95 : 5	91
4	1	1-naphthyl	86	>95 : 5	94
5	1	Me	87	95 : 5	91
6	1	$(CH_2)_2Ph$	78	93	93
7	1	*t*Bu	90	>95 : 5	96[b]
8	1	OEt	77	>95 : 5	91
9	2	Ph	77	90 : 10	89
10	3	Ph	81	86 : 14	75

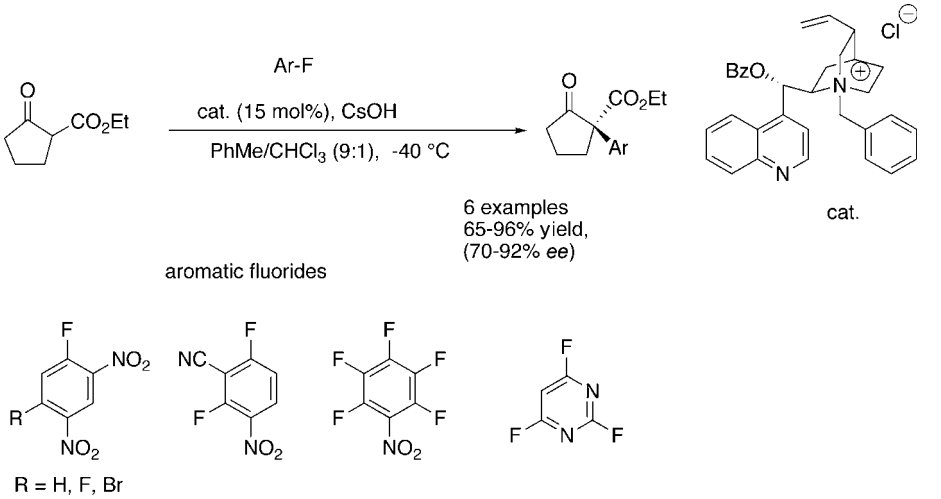
[a] The *ee*-value of *Z*-isomer.
[b] Catalyst loading: 6 mol%.

reaction system. The high diastereoselectivity can be explained by the rapid elimination of ammonium chloride after preferred bond rotation from ammonium enolate intermediates.

Jørgensen and colleagues also demonstrated direct asymmetric α-alkynylation using β-ketoesters with β-halo alkynes, and proposed an addition–elimination mechanism, as outlined in (Scheme 3.20) [43]. This reaction can accommodate a wide range of substrates, including five-, six-, seven-membered and aromatic conjugated ketoesters. When the electron-withdrawing group is an allyloxy carbonyl moiety, its facile removal under Pd catalysis gives α-ethynyl products. These highly enantioselective reactions



Scheme 3.20 Direct asymmetric alkynylation and proposed reaction pathway.

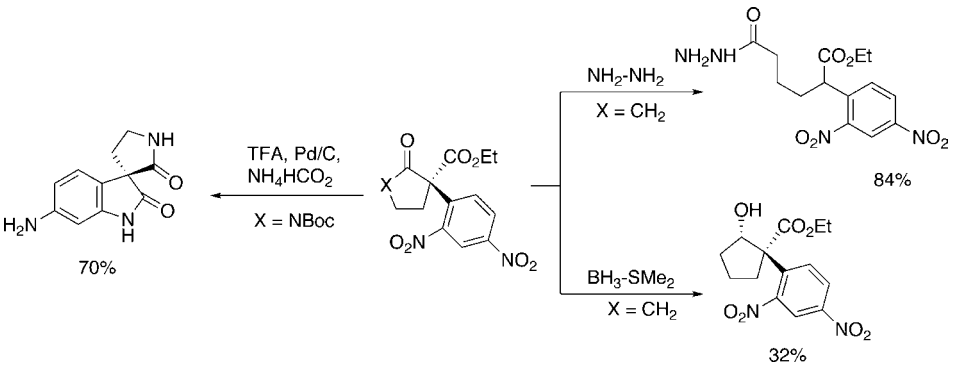


Scheme 3.21 Asymmetric aromatic substitution using fluorobenzenes.

(catalytic vinylic and acetylenic substitution) provide easy accesses to highly functionalized asymmetric quaternary allylic and propargylic stereocenters, and clearly enhance the value of asymmetric phase-transfer catalysis as one of the more powerful synthetic tools.

3.8
Asymmetric S_N Aromatic Reaction

Fluorinated nitrobenzenes are highly activated electrophiles, and have been used in PTC-catalyzed nucleophilic aromatic substitution by Jørgensen and colleagues [44,45]. The arylation ratio at *C*- or *O*- is heavily dependent on the catalyst structure, counter anion and reaction temperature, and the reaction of ketoesters

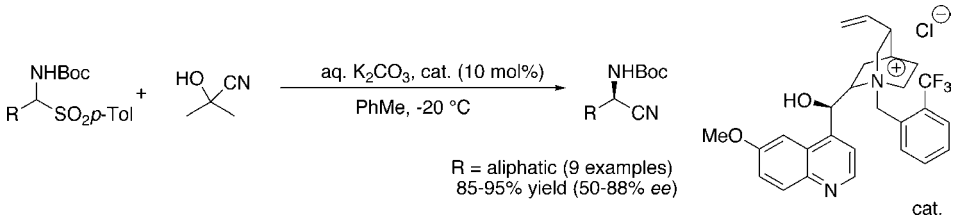


Scheme 3.22 Synthetic application of arylated products.

with various aromatic fluorides proceeds at −40 °C to produce enantiocontrolled adducts bearing asymmetric quaternary carbon in 70 to 92% *ee* (Scheme 3.21). Other nucleophiles such as lactam and cyanoketone can also be used in this asymmetric protocol. The synthetic application of the *C*-adducts is outlined in Scheme 3.22; a spirooxyindole was obtained in 70% yield by one-pot synthesis (N-Boc removal, reduction of two nitro groups followed by cyclization), a ring-opening reaction by hydrazine, and a diastereoselective reduction of ketone have been achieved.

3.9
Asymmetric Strecker Synthesis

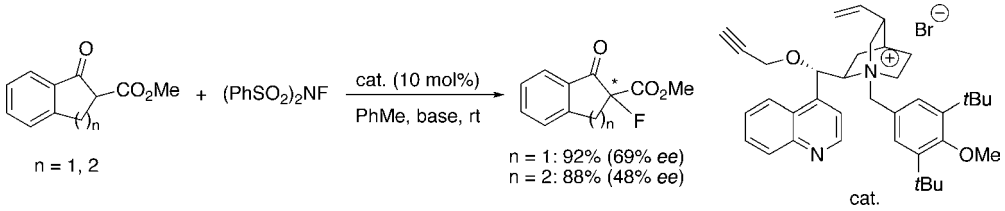
α-Aminonitriles are versatile precursors for α-amino acids, and thus their facile preparation in an optically active form is an important issue in synthetic organic chemistry. α-Amido sulfones, which are effective precursors for the generation of imines, react with acetone cyanohydrin, which is considered to be an inexpensive, easily handled and quite soluble cyanide source, to produce aminonitriles with broad generality in 50 to 88% *ee* (Scheme 3.23) [46]. A similar protocol using KCN and TMSCN resulted in a lower ee-value.



Scheme 3.23 Asymmetric Strecker synthesis using α-amido sulfones with acetone cyanohydrin.

3.10
Asymmetric Fluorination

Organofluorine compounds, and in particular those with a fluorine atom bonded directly to a stereogenic center, are attractive biological tools, and their preparation is



Scheme 3.24

an important issue in medicinal and agrochemistry. Kim reported the electrophilic fluorination of β-ketoesters with $(PhSO_2)_2NF$. As observed in cinchona-alkaloid PTC reactions, an aromatic moiety is important for achieving a higher enantioselectivity and products using indanone, and tetralone derivatives are obtained in respective ee-values of 69% and 48% (Scheme 3.24) [47].

A wide variety of catalytic asymmetric transformations have been achieved in the above investigations, which clearly indicates that quaternary ammonium salts derived from cinchona alkaloids are still powerful reagents, despite their limited structural diversity. Moreover, as PTC chemistry has been recognized as a highly practical approach, further progress should be expected in this area of research.

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4
Cinchona-Derived Chiral Poly(Phase-Transfer Catalysts) for Asymmetric Synthesis

Sang-sup Jew and Hyeung-geun Park

4.1
Cinchona Alkaloids

4.1.1
Cinchona Alkaloids in Asymmetric Phase-Transfer Catalysis

Cinchona alkaloids have been extensively used in the fields of organic chemistry and medicine. In particular, they have achieved major distinction in the area of asymmetric synthesis, where they usually participate in such synthetic methods as an efficient chiral ligand or catalyst [1]. The reason for these materials being one of the essential factors in asymmetric organic reactions is their unique structural nature. Cinchona alkaloids have a quite sterically hindered tertiary amine (Figure 4.1) which is employed as various ligands in heavy metal-mediated reactions or in organocatalytic reactions. In addition, the tertiary amine is frequently derivatized to provide a variety of quaternary ammonium salts serving as efficient phase-transfer catalysts (PTCs). Besides the bridgehead tertiary amine, cinchona alkaloids also have useful functional groups such as the 9-hydroxy group, the 6′-methoxy group in the quinoline ring, and the 10,11-vinyl group in the quinuclidine moiety, all of which sometimes play critical roles in chirality-creating steps, either as themselves or in chemically modified forms. These various advantages render the parent natural cinchona alkaloids as valuable sources in the field of asymmetric organic synthesis. Moreover, the fact that both pseudoenantiomeric forms are available commercially, and at low cost, are additional major attractions for their utilization.

Cinchona alkaloids, of course, have occupied the central position in the design of chiral PTCs. By employing a simple chemical transformation of the tertiary amine of the natural cinchona alkaloids to the corresponding quaternary ammonium salts, using active halides (e.g., aryl-methyl halides), a basic series of PTCs can be readily prepared. Cinchona alkaloid-derived PTCs have proved their real value in many types of catalytic asymmetric synthesis, including: α-alkylation of modified α-amino acids for the synthesis of higher-ordered α-amino acids [2], α-alkylation of

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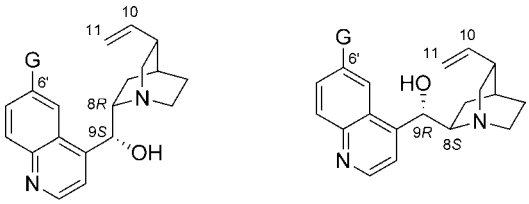
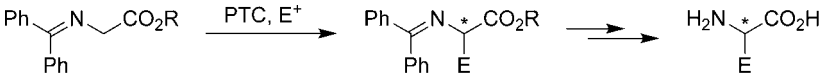


cinchonidine (G = H)
quinine (G = OMe)

cinchonine (G = H)
quinidine (G = OMe)

Figure 4.1 The representative cinchona alkaloids.

enolizable carboxylic esters [3], the Michael reaction [4], aldol reaction [5], Darzens reaction [6], and the epoxidation of enones [8]. To date, one of the most successful uses of cinchona-PTCs has been the preparation of non-natural α-amino acid derivatives (Scheme 4.1) [2]. The use of benzophenone imine of glycine derivatives **A** as substrate in enantioselective monoalkylation under catalytic phase-transfer conditions has been developed into an excellent method for the preparation of a wide range of optically active α-amino acid derivatives, with high chemical yield and enantioselectivity.



A (**1**, R = *t*-Bu) **B** (**2**, R = *t*-Bu) α-Amino acids

Scheme 4.1 Synthesis of α-alkyl-α-amino acids via asymmetric phase-transfer catalytic alkylation of benzophenone imine glycine ester (**A**).

4.1.2
The Origin of Stereoselectivity of Cinchona-PTCs

It is generally considered that a quaternary ammonium salt derived from cinchona alkaloids has an imaginary tetrahedron composed of four carbon atoms adjacent to the bridgehead nitrogen. As shown in Figure 4.2, in order to serve as an efficient

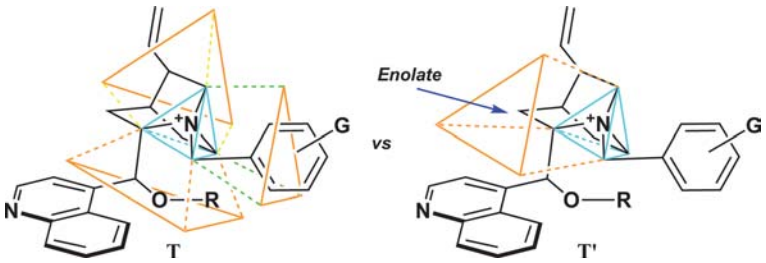


Figure 4.2 Origin of stereoselectivity of cinchona-derived quaternary ammonium salts.

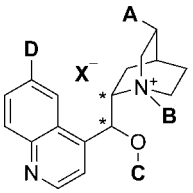
catalyst in asymmetric reactions (particularly in the alkylation of **A**), the cinchona-derived PTC should be designed to provide effective steric screening that can inhibit an approach of the enolate of **A** to three faces of this tetrahedron (**T**), while the remainder should be sufficiently open to allow close contact between enolate anion and ammonium cation (**T′**).

4.2
Development of Dimeric Cinchona-PTCs by the Park-Jew Group

Despite such numerous and fruitful studies having been conducted on the asymmetric phase-transfer catalytic reactions, the development of cinchona-PTCs has, until the start of the 21st century, been mainly focused on the *monomeric* cinchona-PTCs (Figure 4.3).

The development of *polymeric* cinchona-derived PTCs was triggered by the group of Jew and Park in 2001 [8]. The group paid particular attention to the fact that the cinchona alkaloids have demonstrated great utility in the Sharpless asymmetric dihydroxylation. Especially, it was noted that the significant improvements in both stereoselectivity and scope of the asymmetric dihydroxylation were achieved when the dimeric ligands of two independent cinchona alkaloid units attached to heterocyclic spacers were used, such as $(DHQ)_2$-PHAL or $(DHQD)_2$-PYR (Figure 4.4) [9].

The Park–Jew group applied this advantage of dimerization to the design of dimeric cinchona-derived quaternary ammonium salts. The general structure of the designed dimeric cinchona-PTCs is depicted in Figure 4.5; this can be prepared by attaching an appropriate linker such as an aromatic ring to the bridgehead nitrogen of the two cinchona units.



A : vinyl, ethyl, etc.
B : methyl, benzyl, substituted benzyl, anthracenylmethyl, etc.
C : hydrogen, allyl, benzyl, etc.
D : hydrogen, methoxy, etc.
X : halogens

Figure 4.3 Monomeric cinchona-phase-transfer catalysts (PTCs).

4.2.1
Dimeric Cinchona-PTCs with Phenyl Linker

The first series of the dimeric cinchona-PTCs (**3**–**8**) to have a phenyl ring as a linker was designed to examine the primary effect according to the relationship of the attached position (Figure 4.6). One of the two independent cinchona alkaloid units can be located at the *ortho*-, *meta*-, or *para*-position against the other, respectively. The group envisaged that, both chemical yield and enantioselectivity of the asymmetric alkylation of **1** should be affected by the direction of each of the cinchona units.

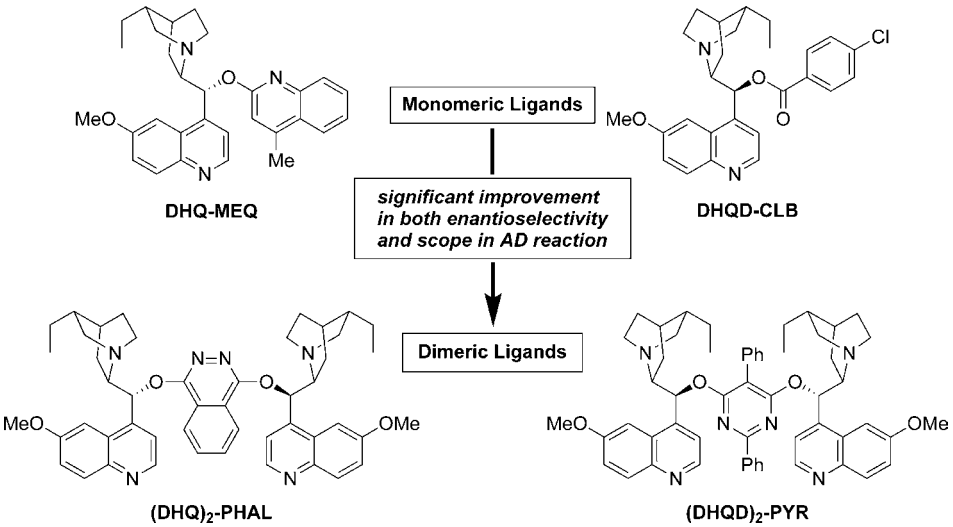


Figure 4.4 Dimerization effects in Sharpless asymmetric dihydroxylation.

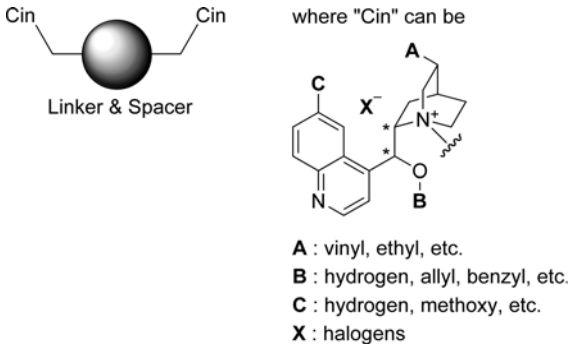


Figure 4.5 General structure of dimeric cinchona-PTCs.

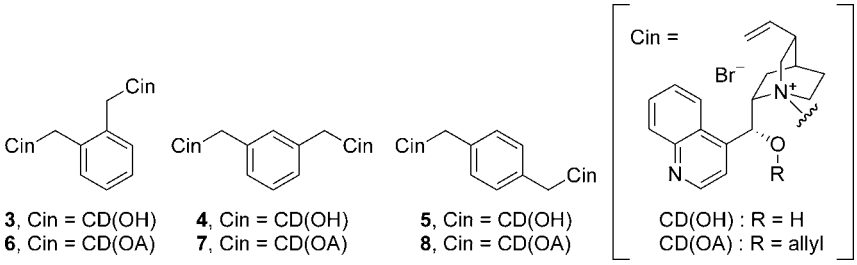
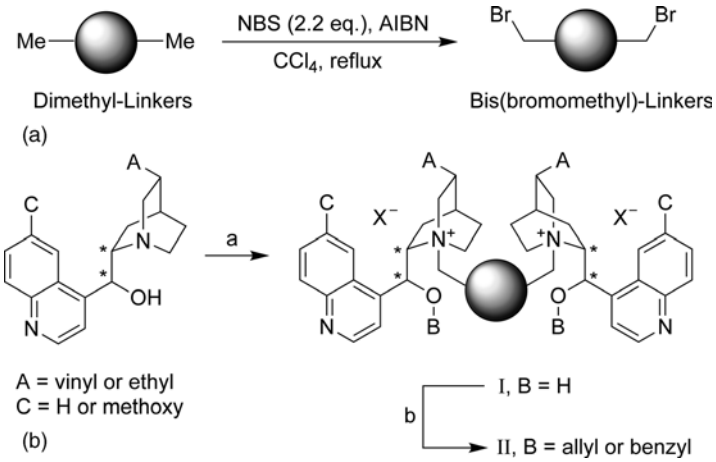


Figure 4.6 The dimeric cinchona-PTCs with phenyl linker.

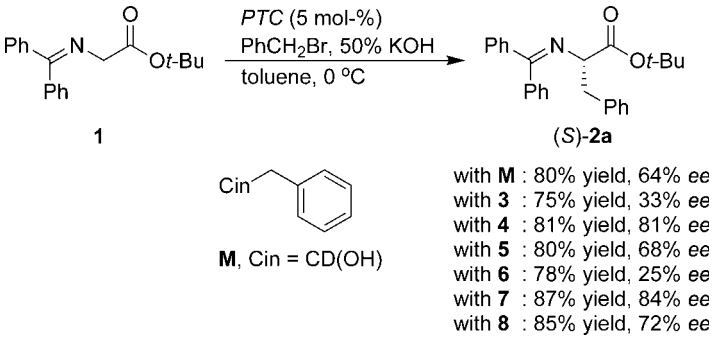


Scheme 4.2 General synthetic scheme for cinchona-derived dimeric quaternary ammonium salts. (a) bis(Bromomethyl)-linkers (0.5 equiv.), EtOH-DMF-$CHCl_3$ (5:6:2), r.t. or reflux. (b) Allyl bromide or benzyl bromide (6.0 equiv.), 50% KOH (10.0 equiv.), CH_2Cl_2, r.t.

Most of the dimeric cinchona-PTCs can be prepared according to (Scheme 4.2a,b). Natural or modified cinchona alkaloids can easily be quaternarized by a reaction with various polyhalo-linkers in EtOH-DMF-$CHCl_3$, and further chemical variation at the 9-hydroxyl position is frequently performed to afford the corresponding allyl or benzyl ether for better catalytic efficiency. One of the distinguished advantages of cinchona-PTCs is that most of the polymeric, as well as the monomeric, forms can be prepared in short steps with good chemical yields. Moreover, generally high purities of the prepared salts can also be achieved by using simple recrystallization processes.

As (−)-cinchonidine-derived ammonium salts have been mainly used as chiral PTCs in monomeric cinchona-PTCs *via* the asymmetric alkylation of **1**, and have generally shown better results than those of others [e.g., derived from (+)-cinchonine, (−)-quinine, and (+)-quinidine], the Park–Jew group primarily prepared (−)-cinchonidine derivatives to identify both the optimal linker and best relationship of attachment for the two cinchona units, and to compare catalytic efficiency with that of monomeric cinchona-PTCs.

From an evaluation of the catalytic efficiency of **3**–**5** using standard catalytic phase-transfer benzylation of **1**, it was found that all compounds had the ability to catalyze this phase-transfer benzylation, and in all cases the (*S*)-isomer of the benzylated imine **2a** was formed in excess (Scheme 4.3). The 1,3-phenyl-linked dimeric PTC **4** showed the highest enantioselectivity among the three dimeric PTCs. The order of enantioselectivity of the three PTCs, along with the monomeric PTC **M**, was as follows: 1,3-dimeric PTC **4** > 1,4-dimeric PTC **5** ≅ monomeric PTC **M** ≫ 1,2-dimeric PTC **3**.



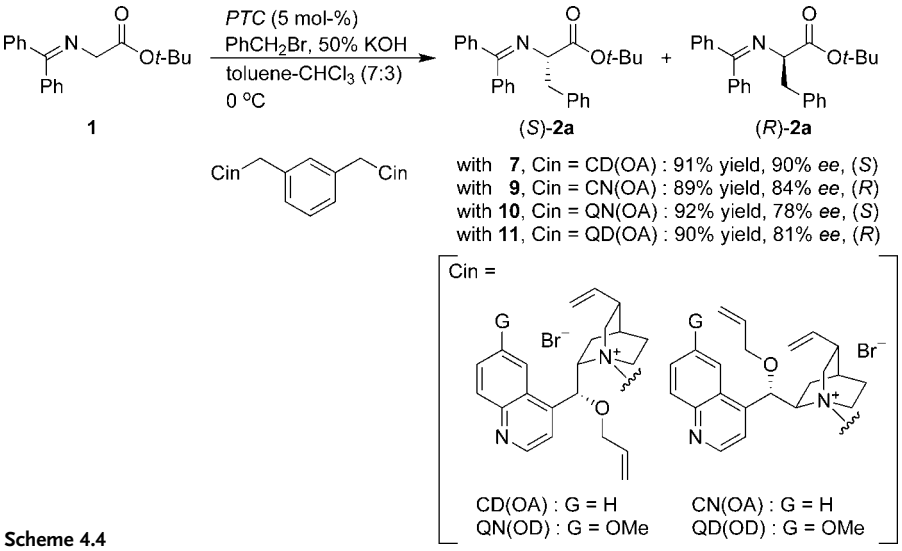
Scheme 4.3

The lack of any difference in enantioselectivity between the 1,4-phenyl-dimeric PTC **5** and the monomeric PTC **M** implies that the two cinchona alkaloid units of the 1,4-phenyl-dimeric PTC do not sterically affect each other. In the case of 1,2-phenyl-dimeric PTC **3**, the severe steric repulsion between the two cinchona alkaloid units may lead to an unfavorable conformation, thereby affording poor enantioselectivity.

The *O*(9)-allyl catalysts were then prepared by allylation of the two 9-hydroxyl groups in the PTCs **6–8** to determine whether the advantages of the *O*(9)-allyl moiety shown in monomeric cinchona-PTCs would be reproduced. Generally, when the 9-hydroxy group is converted to its allyl (or benzyl) ether, the more effective screening of the bottom face of the tetrahedron **T** (as shown in Figure 4.2**)** will function. Moreover, the *O*(9)-alkyl moiety provides an improved solubility of the catalyst in the organic solvents most often used in alkylation, thus affording faster reaction rates and higher chemical yields. A similar tendency was demonstrated in the dimeric PTC system, with the chemical and optical yields obtained by using the allylated PTCs being generally higher than for the non-allyl PTCs, under the same reaction conditions (Scheme 4.3). In the case of the 1,2-dimeric catalysts (**3** versus **6**), however, a decrease in enantioselectivity occurred. This could be explained by there being a more severe steric repulsion between the two-cinchona alkaloid units as a result of the *O*(9)-allylation.

By screening solvent and inorganic bases to establish the optimal reaction conditions for dimeric chiral PTCs, a toluene:chloroform (7 : 3, v/v) solvent system and a 50% aqueous KOH base were found to afford the best enantioselectivity and chemical yield within a reasonable reaction time. As dimeric cinchona-PTCs are very poorly soluble in toluene (one of the popular solvents in asymmetric alkylation), this might act as an obstacle for the catalyst to show its maximum ability. However, the addition of chloroform to toluene provided better results due to an improved solubility of the dimeric PTC. This difference in ability to dissolve the dimeric PTC might be heavily associated not only with the reaction rate but also with the chemical/optical yield. However, the use of chloroform alone proved to be inadequate as an optimal solvent [10].

The effect of the nature of the cinchona alkaloid component was then investigated (Scheme 4.4). The cinchonine-derived PTC **9**, which are in pseudoenantiomeric relationship to the cinchonidine-derived compound **7**, produced the opposite



Scheme 4.4

enantioselectivity, despite the enantiomeric excess (ee) being rather low in the alkylation reaction. The quinine and quinidine derivatives **10** and **11** were found to be less effective [10].

The probable structure of the 1,3-phenyl-dimeric catalyst **4** is shown in Figure 4.7. This is based on the results of an X-ray crystallographic study in which the conformation of the two cinchona alkaloid units are placed in a direction of *anti*-relationship to each other. The figure also shows that each cinchona alkaloid unit

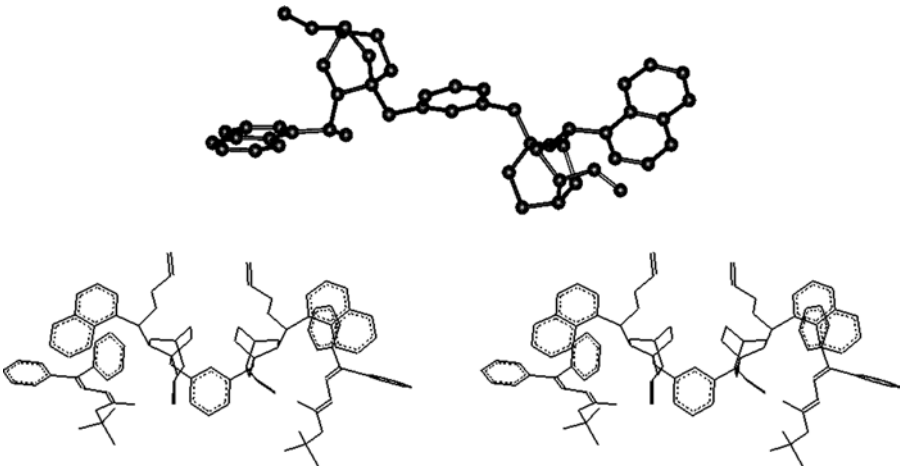


Figure 4.7 The probable structure of the dimeric cinchona-PTC **4** (top), and a stereoview of a plausible model of the preferred three-dimensional arrangement of the ion pair from **7** and one (or two) *E*-enolate(s) of **1**, based on an understanding of the enantio-selectivity (bottom).

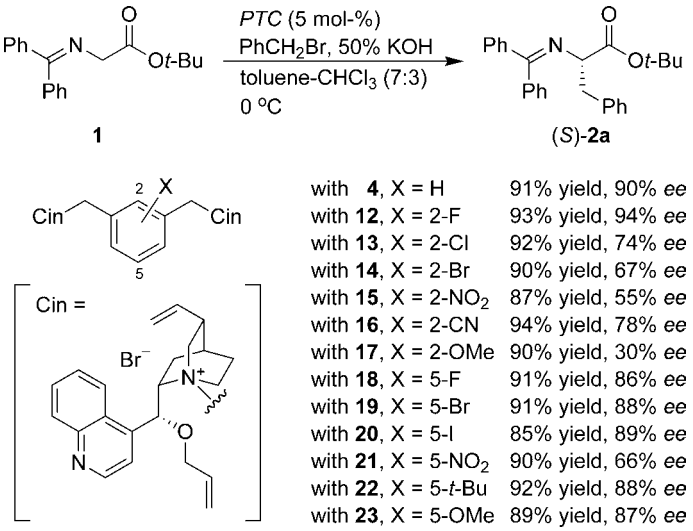
has the same conformation, and is situated in an identical circumstance. Therefore, the same result will be obtained even if an anion such as an enolate of glycine-imine **1** were to approach either of the two ammonium sites of the dimeric catalyst. Unlike the monomeric catalyst **M**, the rotations of the phenyl ring in the dimeric catalyst **4** become restricted, especially when two cinchona alkaloid units are connected through the phenyl spacer in the *meta*-direction. The bulkiness of the cinchona alkaloid unit can obstruct free rotation of both the N^+-CH_2 (benzylic) bond and CH_2 (benzylic)−C (phenyl) bond. This can make the whole conformation of the dimeric catalyst **4** rigid, thus providing the efficient blockade of one face among the four faces of an imaginary tetrahedron against the access of enolate to the bridgehead nitrogen cation. Moreover, another face around the ammonium cation (N^+) can be effectively screened by the quinuclidine ring system itself, while the *O*(9)-allyl moiety also provides an effective additional screening of another face in the case of the *O*(9)-allylated catalyst, such as **7**. Consequently, the remaining face may be open to approach of the enolate of **1** to N^+ to create an ion pair, the result being enantioselective alkylation. Taking the above results together, the presumed transition state, calculated by energy minimization methods, is presented as shown in Figure 4.7. For steric reasons, the electrophile can approach only to the *si* face of the enolate, and this leads to high enantioselectivity [10].

4.2.2
1,3-Dimeric Cinchona-PTCs with Electronically Modified Phenyl Linker

A series of *meta*-dimeric cinchona-PTCs (**12–23**) having electronically modified phenyl linkers were prepared to study the electronic effect in the alkylation of **1** (Scheme 4.5) [11]. Whilst no significant electronic effect on enantioselectivity was observed in the series of 5-substituted derivatives (**18–23**), the enantioselectivities generally decreased in proportion to the bulkiness of the functional group, rather than to the electronic properties in the case of the 2-substituted PTCs. Among this series, the 2-F-substituted compound **12** showed an enhanced result as compared to that of the parent PTC **4**, which is in accordance with the Park–Jew group's finding during the course of study on the effect of electronic factors in monomeric PTCs [12]. It was proposed that the aromatic F might be involved in internal hydrogen bonding involving water, in order to maintain a more rigid and beneficial catalyst conformation. The corresponding 2-F-PTC derived from (+)-cinchonine gave (*R*)-**2a** in a slightly less enantioselectivity (89% ee) compared to **12**.

4.2.3
Polymeric Cinchona-PTCs with Other Linkers

The Park–Jew group next turned their attention towards investigating other linkers besides the phenyl moiety, the aim being to develop more efficient and practical catalysts, such as biphenyls (**24–26**), alkenes and alkynes (**27–29**), naphthalenes (**30–35**), and trimeric catalysts (**36**) (Figure 4.8) [10]. All of the designed PTCs were easily prepared in (generally) good yields according to (Scheme 4.2a, b). The efficacy of these PTCs was



Scheme 4.5

evaluated by the phase-transfer benzylation of **1**, and the results are summarized in Scheme 4.6. Catalysts containing symmetric biphenyl linkers (**24**–**26**) showed dramatic differences according to the substituted position of cinchona alkaloid moieties to the linker. The sterically hindered 2,2′-biphenyl-linked catalyst **24** showed poor activity, while the 3,3′- and 4,4′-biphenyl-linked catalysts **25** and **26** were able effectively to catalyze the reaction, with moderate enantiomeric excesses. Generally low enantioselectivities were obtained when employing the acyclic linkers as in **27**–**29**.

In the cases of catalysts containing the naphthalene linker (**30**–**35**), the 1,4-, 1,5-, and 2,7-substituted catalysts **30**, **31** and **35** gave good enantioselectivities [13]. Whereas, the 2,6-substituted catalyst **34** yielded a moderate result, the sterically hindered catalysts **32** and **33** showed poor enantioselectivities. Especially, the 2,7-naphthalene-linked catalyst **35** was found to possess excellent catalytic activity for this alkylation from the viewpoints of enantioselectivity and chemical yield.

Based on the fact that the *meta*-relationship in catalyst **7** showed good activity in asymmetric alkylation, the same concept was applied to the 1,3,5-trimeric catalyst **36**, in which all cinchona units on the phenyl ring were placed in the *meta*-position to each other; hence, it would be expected this relationship might increase or maintain the catalytic efficiency of the *meta*-dimeric effect. Compared with the result from **7**, the effect of trimerization could be regarded as quite similar to that of the *meta*-directing-dimerization in chemical and optical yields [14].

4.2.4
1,3-Phenyl- and 2,7-Naphthyl-Linked Dimeric Cinchona-PTCs

In the Park–Jew group's systematic investigation, two types of catalyst – the 1,3-phenyl- and 2,7-naphthyl-based dimeric ammonium salts – were selected as an efficient skeleton of chiral PTCs for the catalytic asymmetric phase-transfer alkylation

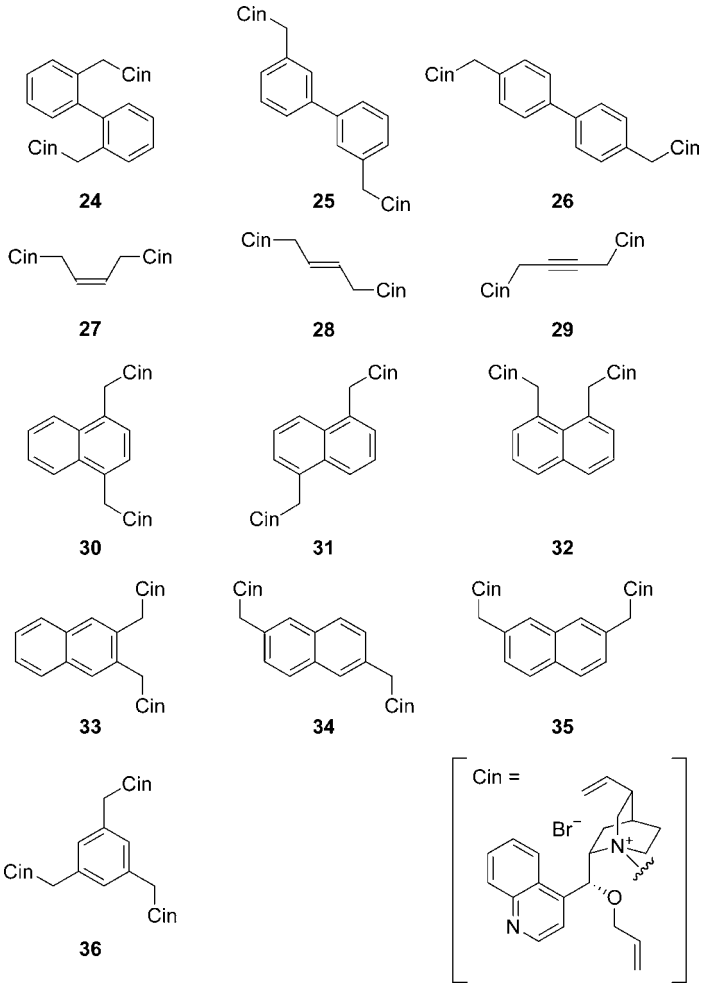
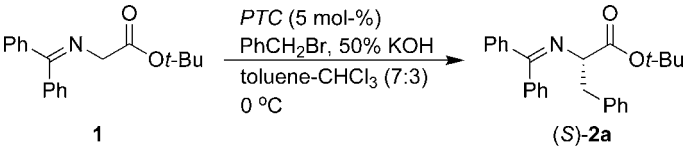


Figure 4.8 Polymeric cinchona-PTCs with other linkers.

of the benzophenone imine of glycine derivative **1**. Subsequently, the 10,11-hydro-derivatives were adopted in order to obtain maximum results, and antipodal *R*-amino acid derivatives were expected to be obtained in excess simply by changing the cinchona alkaloid to a hydrocinchoninium component. By using selected hydro-catalysts (**37–40**; Figure 4.9), the Park–Jew group performed further studies on the reaction conditions by varying reaction temperature and loading amount of PTC to identify the optimal reaction conditions (Scheme 4.7). The use of naphthalene-linked catalysts (**39**, **40**) compared to benzene-linked catalysts (**37**, **38**), coupled with the lower reaction temperature, provided slightly higher enantioselectivities. Thus, optically enriched (*R*)-α-amino acid derivatives were obtained using hydro-cinchoninium derivatives (**38** or **40**), with satisfactory enantiomeric excesses of up to 96%. In particular, when the 2,7-naphthalene-linked dimeric catalyst **39** was employed at



with **24**, 80% yield, 25% *ee*
with **25**, 85% yield, 80% *ee*
with **26**, 87% yield, 82% *ee*
with **27**, 92% yield, 19% *ee*
with **28**, 90% yield, 24% *ee*
with **29**, 86% yield, 10% *ee*

with **30**, 94% yield, 91% *ee*
with **31**, 94% yield, 89% *ee*
with **32**, 85% yield, 27% *ee*
with **33**, 90% yield, 22% *ee*
with **34**, 89% yield, 70% *ee*
with **35**, 94% yield, 94% *ee*
with **36**, 95% yield, 91% *ee*

Scheme 4.6

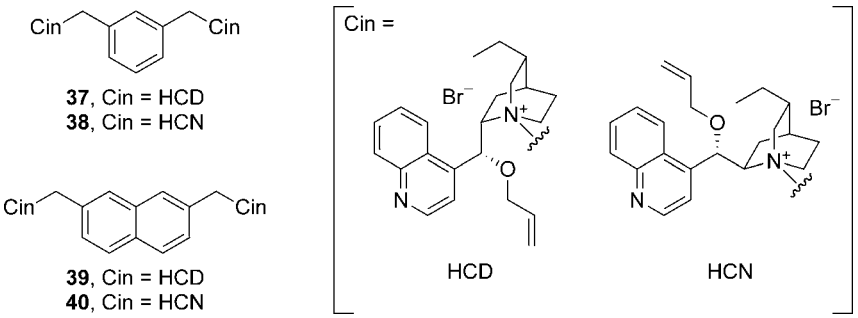
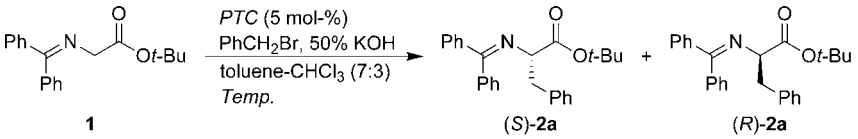


Figure 4.9 The selected highly efficient dimeric PTCs for the asymmetric synthesis of α-amino acids.



with **37**
at r.t. : 2 h, 91% yield, 90% *ee*, (*S*)
at 0 °C : 4 h, 94% yield, 93% *ee*, (*S*)
at 0 °C* : 10 h, 92% yield, 93% *ee*, (*S*)
at -20 °C : 6 h, 94% yield, 96% *ee*, (*S*)
at -40 °C : 18 h, 90% yield, 98% *ee*, (*S*)
[* 1 mol-% of **37**]

with **38**
at r.t. : 3 h, 94% yield, 83% *ee*, (*R*)
at 0 °C : 3 h, 93% yield, 86% *ee*, (*R*)
at 0 °C* : 12 h, 90% yield, 86% *ee*, (*R*)
at -20 °C : 10 h, 92% yield, 92% *ee*, (*R*)
at -40 °C : 30 h, 85% yield, 94% *ee*, (*R*)
[* 1 mol-% of **38**]

with **39**
at r.t. : 0.05 h, 95% yield, 92% *ee*, (*S*)
at 0 °C : 0.5 h, 95% yield, 98% *ee*, (*S*)
at 0 °C* : 10 h, 95% yield, 98% *ee*, (*S*)
at -20 °C : 6 h, 93% yield, 99% *ee*, (*S*)
at -40 °C : 20 h, 90% yield, >99% *ee*, (*S*)
[* 1 mol-% of **39**]

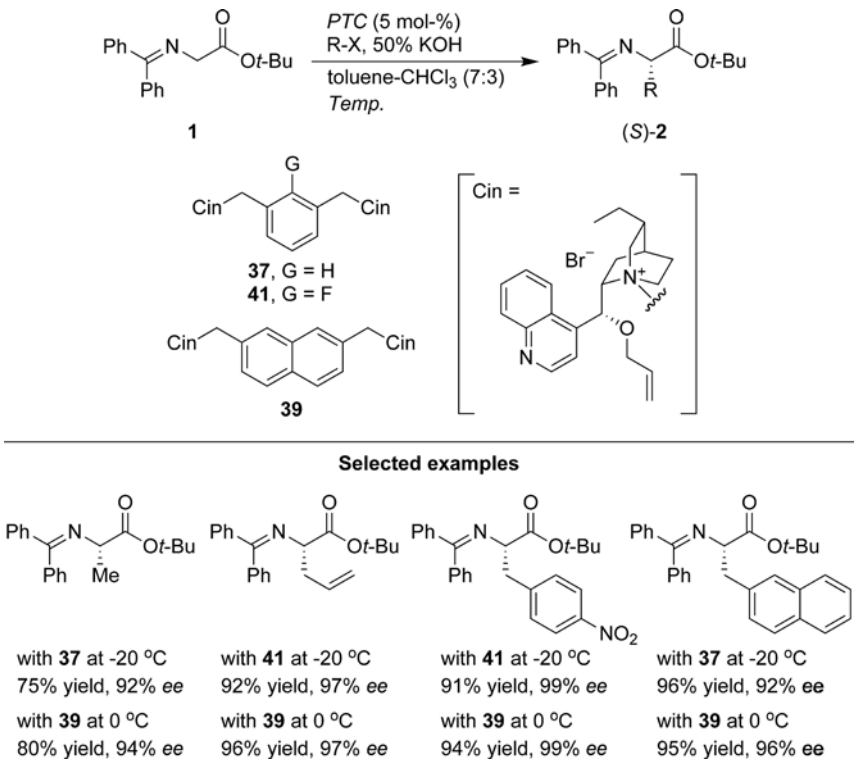
with **40**
at r.t. : 2 h, 94% yield, 91% *ee*, (*R*)
at 0 °C : 3 h, 92% yield, 93% *ee*, (*R*)
at 0 °C* : 10 h, 91% yield, 93% *ee*, (*R*)
at -20 °C : 8 h, 92% yield, 95% *ee*, (*R*)
at -40 °C : 20 h, 88% yield, 96% *ee*, (*R*)
[* 1 mol-% of **40**]

Scheme 4.7

0 °C, a very high enantioselectivity (98% ee) as well as a high chemical yield (95%) was obtained within a short reaction time (30 min). Notably, all of the PTCs were able to conserve their high catalytic efficiency in terms of both reactivity and enantioselectivity, even when present in smaller quantities (1 mol%).

Interestingly, the molecular structure of the 2,7-naphthyl catalysts **39** and **40** markedly resembles that of the 1,3-phenyl catalysts **37** and **38**, respectively; the only difference is the distance between the two cinchona alkaloid units. The naphthalene linker is about 2.4 Å longer than the benzene linker. The Park–Jew group proposed that the reason for the higher enantioselectivity of the 2,7-naphthyl catalyst was that the 2,7-naphthalene linker might confer a spatial benefit to form a more favorable conformation by decreasing the steric hindrance between the two cinchona units compared to that in the 1,3-benzene linker.

Having optimized the catalytic enantioselective phase-transfer alkylation system, the group explored the scope and limitations. A variety of electrophiles were reacted with the benzophenone imine glycine *tert*-butyl ester **1** catalyzed by 5 mol% of the selected chiral dimeric PTCs, benzene-linked-1,3-dimeric PTC **37**, 2′-F-benzene-linked-1,3-dimeric PTC **41**, and naphthalene-linked-2,7-dimeric PTC **39**, at reaction temperatures of 0 °C or −20 °C (Scheme 4.8).

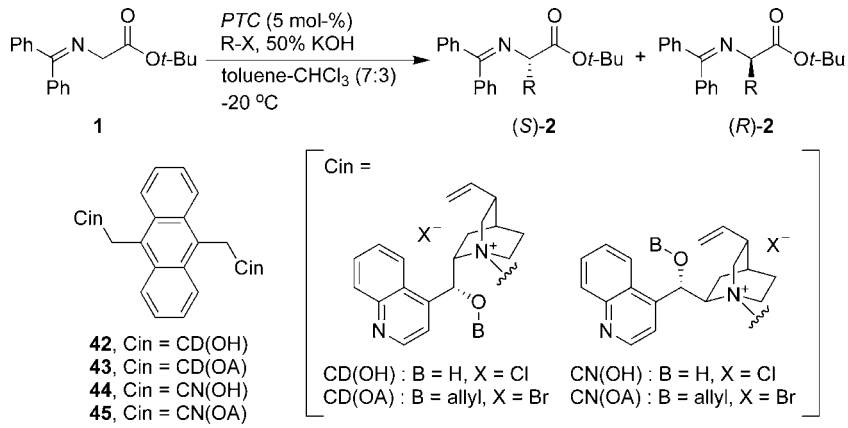


Scheme 4.8

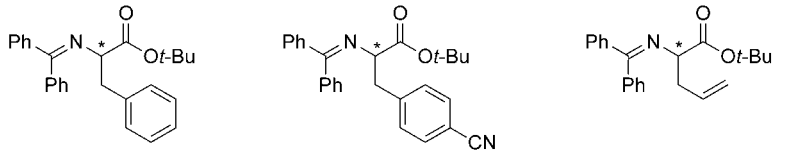
4.3
Polymeric PTCs Developed by the Najera Group

Further structural variations of polymeric cinchona-PTCs based on the Park–Jew group's successful findings were performed by several research teams. The Nájera group envisaged that good results could be obtained if a bulkier 9,10-dimethylanthracenyl group was employed as a spacer between the alkaloid moieties, in analogy to the Lygo's and the Corey's improvements relative to the monomeric catalysts [15]. Thus, they prepared cinchonine- and cinchonidine-versions of the anthracene-linked-dimeric PTCs (**42**–**44**) according to (Scheme 4.2a,b), respectively, and applied them to the asymmetric alkylation of **1** (Scheme 4.9) [16]. However, contrary to their expectations, the level of enantiomeric excess of the alkylated imines **2** was not quite satisfactory.

With these anthracene-linked dimeric cinchona-PTCs, the Nájera group investigated the counterion effect in asymmetric alkylation of **1** by exchanging the classical chloride or bromide anion with tetrafluoroborate (BF_4^-) or hexafluorophosphate (PF_6^-) anions (Scheme 4.10) [17]. They anticipated that both tetrafluoroborate and hexafluorophosphate could form less-tight ionic pairs than chloride or bromide, thus allowing a more easy and rapid complexation of the chiral ammonium cation with the enolate of **1**, and therefore driving to a higher enantioselectivity. However, when

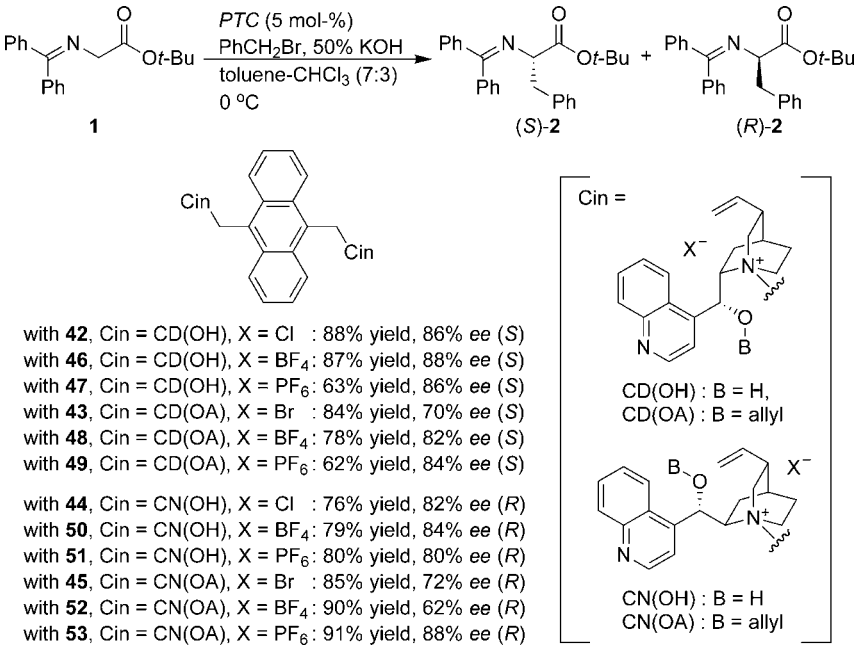


Selected examples



with **42**, 75% yield, 86% *ee* (*S*) with **42**, 90% yield, 90% *ee* (*S*) with **42**, 60% yield, 68% *ee* (*S*)
with **43**, 72% yield, 80% *ee* (*S*) with **43**, 97% yield, 85% *ee* (*S*) with **43**, 70% yield, 42% *ee* (*S*)
with **44**, 85% yield, 86% *ee* (*R*) with **44**, 90% yield, 84% *ee* (*R*)

Scheme 4.9



Scheme 4.10

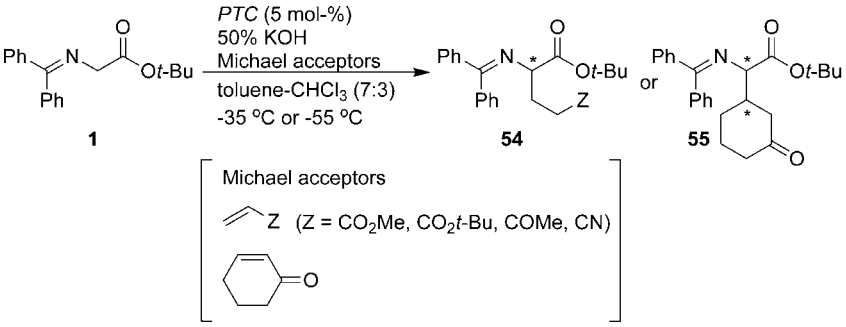
using BF_4^- and PF_4^- derivatives (**47–53**) in the asymmetric benzylation of **1**, the effect of changing the anion was found to be minimal.

These anthracene-linked dimeric PTCs (**42–53**) were also employed in the Michael addition reaction of **1** by the Nájera group (Scheme 4.11) [18]. Depending on the Michael acceptor and the nature of the counter anion part of the ammonium cation in PTC, a variation of both chemical yield and stereoselectivity was observed.

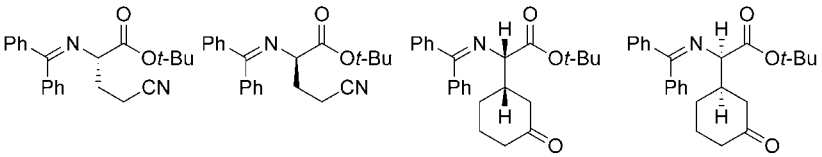
4.4 Polymeric PTCs Developed by the Siva Group

The Siva group reported another type of dimeric cinchona-PTC containing an aliphatic tetra-azacyclotetradecane-based-linker (**56** and **57**), and their application to the asymmetric alkylation of **1** (Scheme 4.12) [19]. In general, high chemical and optical yields were obtained, even with a lower dimeric PTC loading of (1.5 mol%) compared to the more commonly used level (5.0 mol%).

Based on the ongoing investigations of the Siva group to develop polymeric cinchona-PTCs, two types of trimeric cinchona-PTC (**58–60**) were designed (Figure 4.10) [20]. This group also identified the optimal reaction conditions suitable for their trimeric PTCs in the asymmetric alkylation of **1** by the systematic variation of reaction-governing factors such as inorganic base, solvent, reaction temperature, and stirring speed. As shown in Scheme 4.13, the reaction conditions selected were 20% aqueous NaOH in toluene: CH_2Cl_2 (8:2, v/v) at $-10\,^{\circ}C$, with a stirring speed of 400 r.p.m.



Selected examples



with **43**, at -35 °C	with **45**, at -35 °C	with **43**, at -35 °C	with **45**, at -35 °C
82% yield, 72% *ee*,	72% yield, 60% *ee*,	83% yield, 92% *ee*,	92% yield, 90% *ee*,
with **48**, at -35 °C	with **52**, at -35 °C	with **48**, at -35 °C	with **52**, at -35 °C
85% yield, 80% *ee*,	59% yield, 6% *ee*,	57% yield, 76% *ee*,	73% yield, 81% *ee*,
with **49**, at -35 °C	with **53**, at -35 °C	with **49**, at -35 °C	with **53**, at -35 °C
72% yield, 88% *ee*,	70% yield, 79% *ee*,	32% yield, 97% *ee*,	91% yield, 91% *ee*

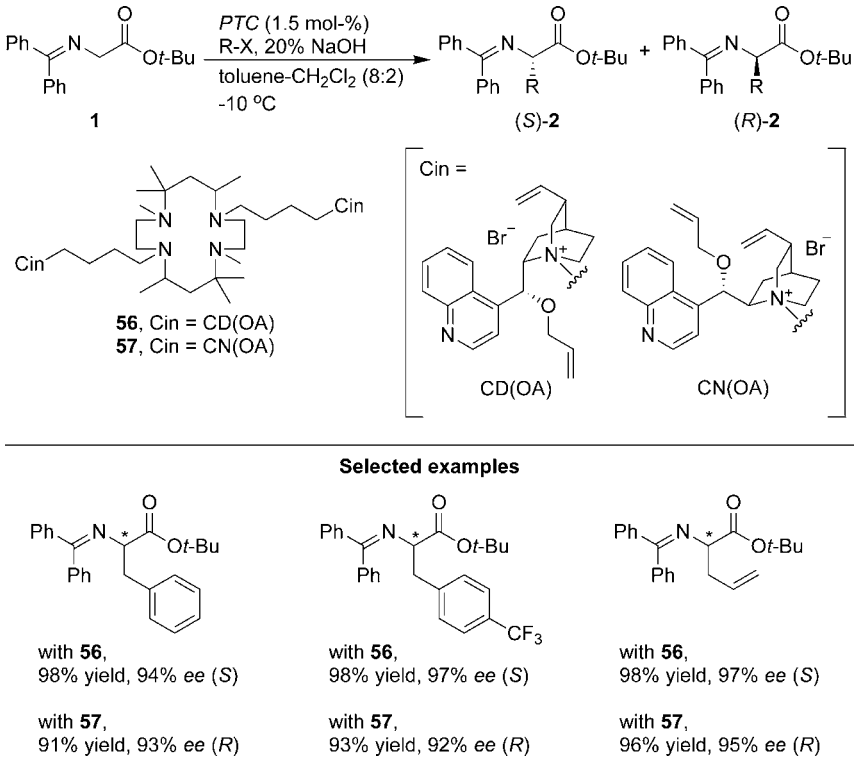
Scheme 4.11

4.5
Polymeric PTCs Developed by the Wang Group

Water-soluble polyethylene glycol (PEG)-supported dimeric cinchona-PTCs (**61**–**63**) were developed by the Wang group (Scheme 4.14) [21]. These are prepared by the reaction of diacetamido–PEG2000 chloride with natural cinchona alkaloid in refluxing chloroform. The polymer-supported dimeric PTCs were found to show better catalytic activity in the asymmetric alkylation of **1** when the solvent was water rather than organic. The interesting feature of these PTC is that a steady chemical yield and enantioselectivity are guaranteed, even after recovery and recycling on several occasions, which in turn suggests that the acetamido-moiety-connected cinchona and PEG might be minimally disintegrated under the mild reaction conditions.

4.6
Asymmetric Epoxidation with Polymeric Cinchona-PTCs

Besides the asymmetric alkylation of **1** for the synthesis of higher α-amino acid derivatives, the Park–Jew group applied their dimeric cinchona-PTCs to the



Scheme 4.12

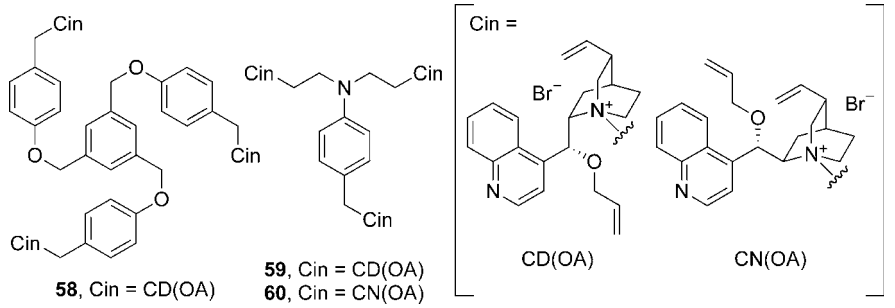
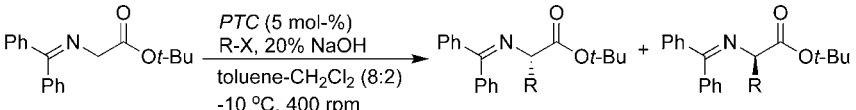
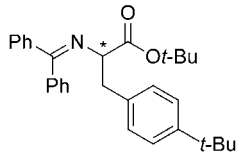


Figure 4.10 Polymeric PTCs developed by the Siva group.

asymmetric epoxidation of 2,4-diarylenones [22]. During the initial stages of these investigations, a low enantioselectivity was obtained with basic dimeric PTC **4** under the given conditions, as shown in Scheme 4.15. It was considered that the long reaction time, caused mainly by the poor solubility of the PTC **4**, had allowed non-PTC-mediated epoxidation to occur, resulting in a low enantioselectivity. However, by employing a surfactant such as Triton X-100, Tween 20 or Span 20, a shorter reaction



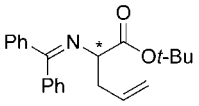
Selected examples



with **58**,
93% yield, 95% *ee* (*S*)

with **59**,
96% yield, 97% *ee* (*S*)

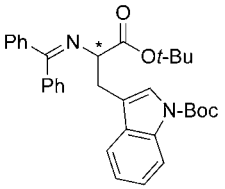
with **60**,
97% yield, 98% *ee* (*R*)



with **58**,
96% yield, 86% *ee* (*S*)

with **59**,
90% yield, 97% *ee* (*S*)

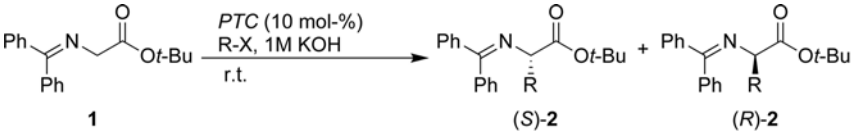
with **60**,
89% yield, 98% *ee* (*R*)

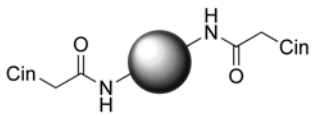


with **59**,
53% ee (*S*)

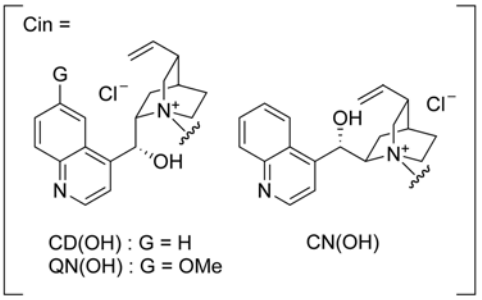
with **60**,
67% ee (*R*)

Scheme 4.13





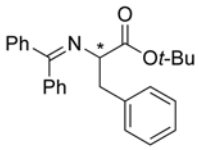
61, Cin = CD(OH)
62, Cin = QN(OH)
63, Cin = CN(OH)



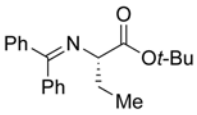
CD(OH) : G = H
QN(OH) : G = OMe

CN(OH)

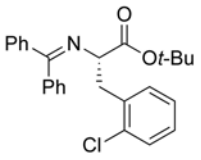
Selected examples



with **61**, 95% yield, 75% *ee* (*S*)
with **62**, 98% yield, 83% *ee* (*S*)
with **60**, 97% yield, 80% *ee* (*R*)

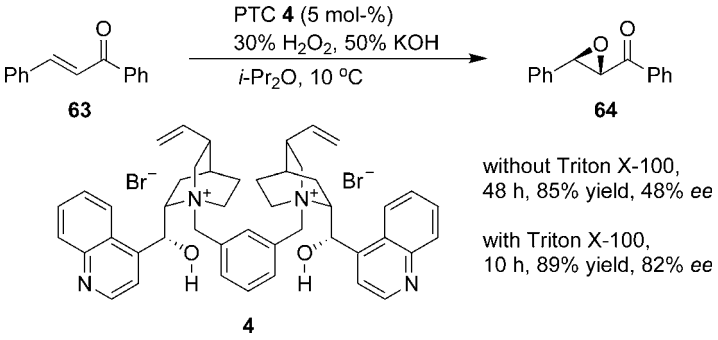


with **62**,
82% yield, 90% *ee*



with **62**,
94% yield, 97% *ee*

Scheme 4.14



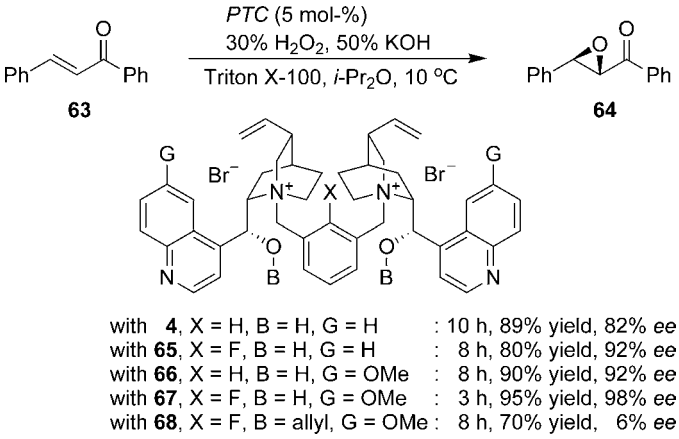
Scheme 4.15

time along with an enhanced enantioselectivity was obtained. Hence, it was proposed that, in cases of slow asymmetric phase-transfer catalytic reactions, the low stereoselectivities may not always reflect the low catalytic efficiencies of the employed catalysts. The low reaction rates might not allow the catalysts to perform optimally; therefore, surfactants might effectively increase the stereoselectivity and allow an accurate evaluation of the catalyst's capacity in phase-transfer catalytic reactions.

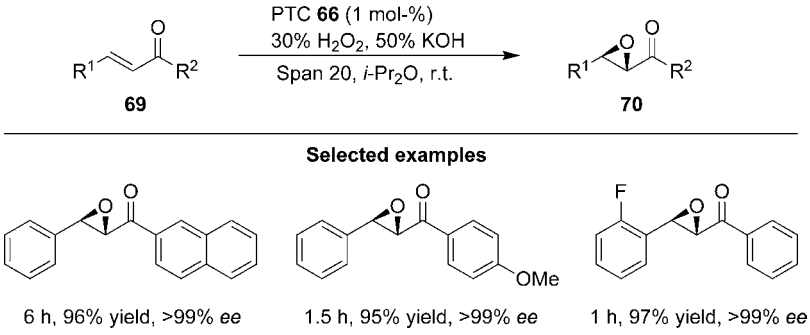
During the search for the optimal dimeric PTC for this epoxidation, the Park–Jew group found an interesting result, namely that the functional groups of 9-OH and 6′-OMe in the cinchona unit, along with 2-F group in the phenyl linker, were critical factors for high enantioselectivity of the reaction (Scheme 4.16).

Under these optimized reaction conditions, highly optically pure α,β-epoxycarbonyl compounds could be obtained, in high chemical yields and over short reaction times and at room temperature, even with 1 mol% loading of **66** (Scheme 4.17).

The Park–Jew group proposed a possible transition state in which the chalcone is located between the two cinchona units in the catalyst **66**, and the β-phenyl moiety of chalcone has a π–π stacking interaction with one of the quinoline moieties in **66**.



Scheme 4.16



Scheme 4.17

The carbonyl oxygen atom is placed as close to the ammonium cation as permitted by the van der Waals forces. The other ammonium cation is ion-paired with the hydrogen peroxide ion through hydrogen bonding with the oxygen of the 6′-OMe group in the quinoline part. As a consequence, the hydrogen peroxide anion can only approach the β carbon atom of chalcone from the upside in the 1,4-addition to afford the α*S*,β*R*-stereoisomer (Figure 4.11).

The Wang group also reported the asymmetric epoxidation of chalcone derivatives with their polymer-supported dimeric PTC **61** using *tert*-butyl hydroperoxide as an oxidant (Scheme 4.18) [23].

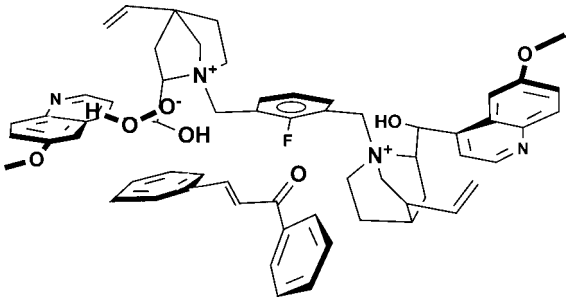
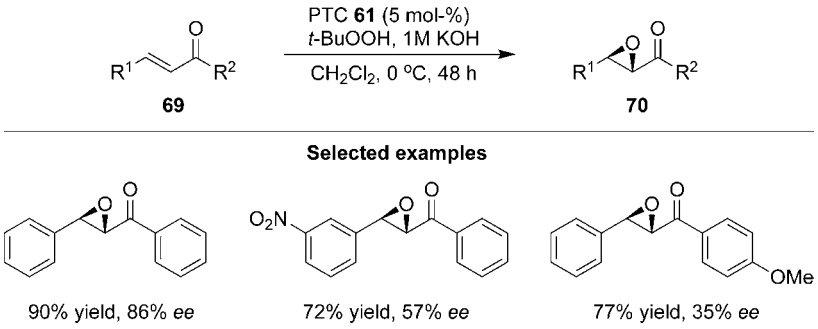


Figure 4.11 Plausible transition state for the asymmetric epoxidation.



Scheme 4.18

4.7 Conclusions

Cinchona alkaloids have proven to be a popular natural source of practical catalysts in a variety of organic reactions used in industrial processes, due largely to their excellent commercial availability and low cost. Phase-transfer catalysis represents one of the most useful methodologies for practical syntheses, because of its operational simplicity and mild reaction conditions which enable its application to industrial processes. Chiral quaternary ammonium salts derived from cinchona alkaloids have been developed and applied successfully to a variety of useful enantioselective phase-transfer catalysis reactions. Among the quaternary ammonium salt catalysts developed to date, polymeric catalysts prepared by the polymerization of cinchona units via spacers have led to considerable increases in the enantioselectivity and scope of the substrate in phase-transfer catalytic reaction. In any phase-transfer catalytic reaction it is difficult to predict which catalyst might be the most efficient, as this depends on the catalyst's ability to form ionic complexes with substrate anions. Thus, with an increasing need to diversify among catalysts, the major challenge for the future will be to identify new polymeric catalysts and corresponding organic reactions.

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5
Binaphthyl- and Biphenyl-Modified Chiral Phase-Transfer Catalysts for Asymmetric Synthesis

Keiji Maruoka

5.1
Introduction

Phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis in both industrial and academic laboratories, based on its simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations [1]. In particular, over the past two decades and more, asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has become a topic of great scientific interest, and recent enormous efforts have resulted in notable achievements, making it feasible to perform a variety of bond-formation reactions under mild phase-transfer-catalyzed conditions [2]. This chapter focuses on recent progress in asymmetric reactions with various types of binaphthyl-modified chiral quaternary ammonium salts of type **1** as chiral phase-transfer catalysts, in particular showcasing the variations in their molecular design and synthetic applications.

5.2
Alkylation

5.2.1
Asymmetric Synthesis of α-Alkyl α-Amino Acids and Their Derivatives

5.2.1.1 Asymmetric Monoalkylation of Glycine Ester Schiff Bases

In 1989, following five years of epoch-making investigations by the Merck group [3], *N*-benzyl cinchoninium halide as a chiral phase-transfer catalyst was successfully utilized by O'Donnell for the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** as a key substrate [4]. Although asymmetric phase-transfer alkylation of glycine Schiff base **2** can be achieved by using chiral phase-transfer catalysts derived from relatively inexpensive, commercially available cinchona alkaloids, the

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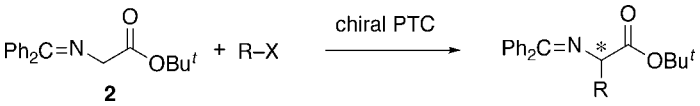
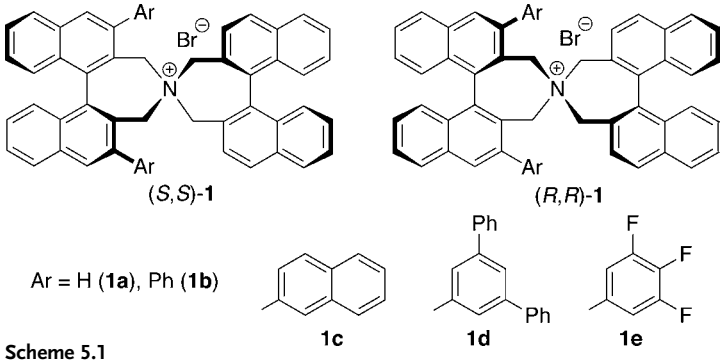
research in this area had made little progress for some time after O'Donnell's milestone reports. However, a new class of cinchona alkaloid-derived catalysts bearing an *N*-anthracenylmethyl function and developed independently by Corey [5] and Lygo [6], have opened a new era of asymmetric phase-transfer catalysis.



2

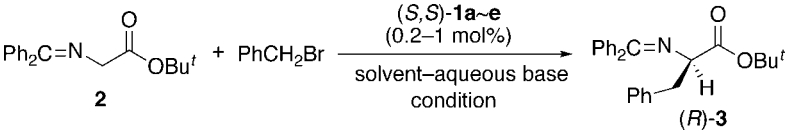
In 1999, in consideration of the readily structural modifications and fine-tuning of catalysts to attain sufficient reactivity and selectivity, Maruoka and coworkers designed and prepared the structurally rigid, chiral spiro ammonium salts of type **1** derived from commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol as a new C_2-symmetric chiral phase-transfer catalyst, and successfully applied this to the highly efficient, catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester under mild phase-transfer conditions (Scheme 5.1) [7].

The key finding was a significant effect of an aromatic substituent (Ar) at the 3,3′-position of one binaphthyl subunit of the catalyst **1** on the enantiofacial discrimination, as shown in Table 5.1. An initial attempt was made on the benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** with 1 mol% of symmetric (*S*,*S*)-**1a** in 50% aqueous NaOH-benzene (1:3, v/v) at room temperature, and the corresponding benzylation product (*R*)-**3** was obtained in 76% yield with 73% *ee* (*R*) (Table 5.1, entry 1). The introduction of an aromatic substituent on the 3,3′-position of one binaphthyl subunit of the catalyst (Ar) afforded a beneficial effect on the enantiofacial discrimination, as the reaction with (*S*,*S*)-**1b** resulted in formation of the product in 43% yield with 81% *ee* (entry 2). The use of toluene as organic solvent at a lower reaction temperature (0 °C) led to even higher enantioselectivity (88% ee) (entry 3). Moreover, the reaction under the influence of (*S*,*S*)-**1b** was completed within 30 min at 0 °C with 50% KOH as an aqueous base, giving the product in 81% yield with 89% *ee* (entry 4). Switching the catalyst to (*S*,*S*)-**1c** and sterically more hindered (*S*,*S*)-**1d** further increased the enantioselectivity to 96% *ee* and 98% ee, respectively (entries 5 and 6), while virtually complete stereochemical control was achieved using (*S*,*S*)-**1e** as catalyst (entry 8). The lower chemical yield of the benzylation with (*S*,*S*)-**1e** was



Scheme 5.1

Table 5.1 Effect of catalyst structure, solvent and aqueous base on the reactivity and selectivity of phase-transfer benzylation of **2**.

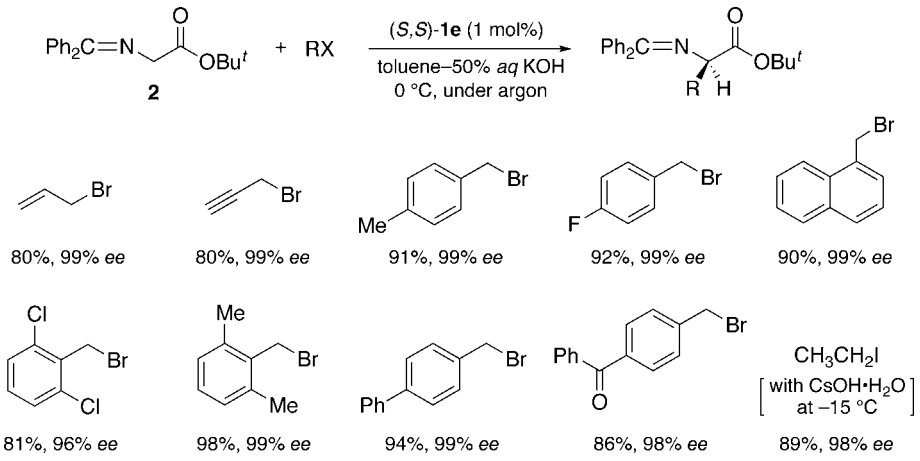


Entry	Catalyst (mol%)	Solvent	Base	Conditions (°C, h)	Yield (%)	*ee* (%) (config.)
1	(*S,S*)-**1a** (1)	Benzene	50% NaOH	r.t.; 10	76	73 (*R*)
2	(*S,S*)-**1b** (1)			r.t.; 10	43	81 (*R*)
3		Toluene		0; 5	62	88 (*R*)
4			50% KOH	0; 0.5	82	89 (*R*)
5	(*S,S*)-**1c** (1)			0; 0.5	95	96 (*R*)
6	(*S,S*)-**1d** (1)			0; 0.5	91	98 (*R*)
7	(*S,S*)-**1d** (0.2)			0; 12	81	98 (*R*)
8	(*S,S*)-**1e** (1)			0; 2	79	99 (*R*)
9[a)]	(*S,S*)-**1e** (1)			0; 12	90	99 (*R*)
10[a)]	(*S,S*)-**1e** (0.2)			0; 48	72	99 (*R*)

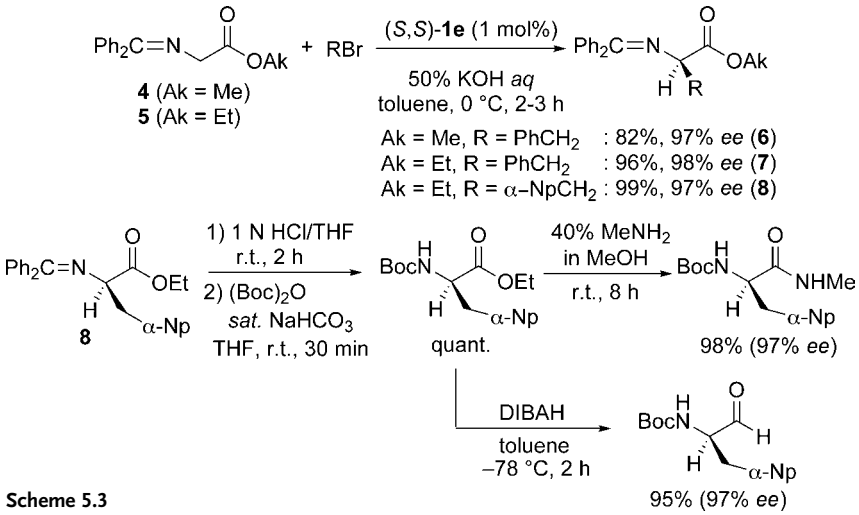
[a)] Under argon atmosphere.
r.t. = room temperature.

ascribed to the intervention of enolate oxidation by aerobic oxygen, and this problem was overcome by simply performing the reaction under an argon atmosphere (entry 9). One notable advantage of this method is that the catalyst loading can be reduced to 0.2 mol%, without any loss of enantiomeric excess (*ee*) (entries 7 and 10) [7e].

(*S,S*)-**1e** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation, as shown in Scheme 5.2.



Scheme 5.2



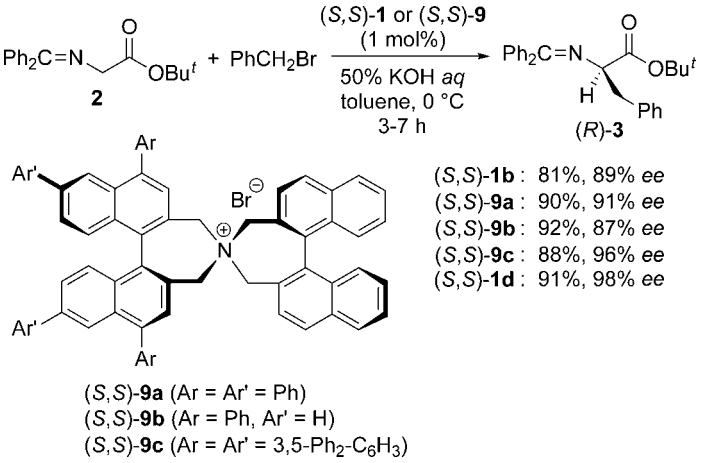
Scheme 5.3

The facile asymmetric synthesis of α-amino acids usually inaccessible by enzymatic processes becomes feasible by employing appropriate electrophiles such as *ortho*-disubstituted benzyl bromides. In the reaction with simple alkyl halides such as ethyl iodide, the use of aqueous cesium hydroxide (CsOH) as a basic phase at a lower reaction temperature is generally recommended [7e].

The salient feature of **1e** as a chiral phase-transfer catalyst is its ability to catalyze the asymmetric alkylation of glycine methyl and ethyl ester derivatives **4** and **5** with excellent enantioselectivities. Since methyl and ethyl esters are certainly more susceptible towards nucleophilic additions than *tert*-butyl ester, the synthetic advantage of this process is clear, and highlighted by the facile transformation of the alkylation products (Scheme 5.3) [8].

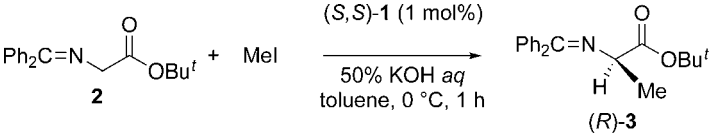
With the critical role of 3,3′-diaryl substituents of **1** in mind, Maruoka and coworkers examined the effect of 4,4′- and 6,6′-substituents of one binaphthyl subunit. As shown in (Scheme 5.4), the introduction of simple aromatic groups even at the 4,4′-position leads to a meaningful effect on the stereoselectivity of the phase-transfer-catalyzed alkylation of **2** [9].

Maruoka and coworkers also investigated the substantial reactivity enhancement of *N*-spiro chiral quaternary ammonium salt and simplification of its structure, the aim being to establish a truly practical method for the asymmetric synthesis of α-amino acids and their derivatives. As ultrasonic irradiation produces homogenization (i.e., very fine emulsions), it greatly increases the reactive interfacial area, which may in turn deliver a substantial rate acceleration in the liquid–liquid phase-transfer reactions. Indeed, sonication of the reaction mixture of **2**, methyl iodide and (*S,S*)-**1c** (1 mol%) in toluene-50% KOH aqueous solution at 0 °C for 1 h gave rise to the corresponding alkylation product in 63% yield with 88% *ee*. Hence, the reaction was speeded up markedly, and the chemical yield and enantioselectivity were comparable with those of the reaction with simple stirring (0 °C for 8 h; 64%, 90% *ee*) (Scheme 5.5) [10].

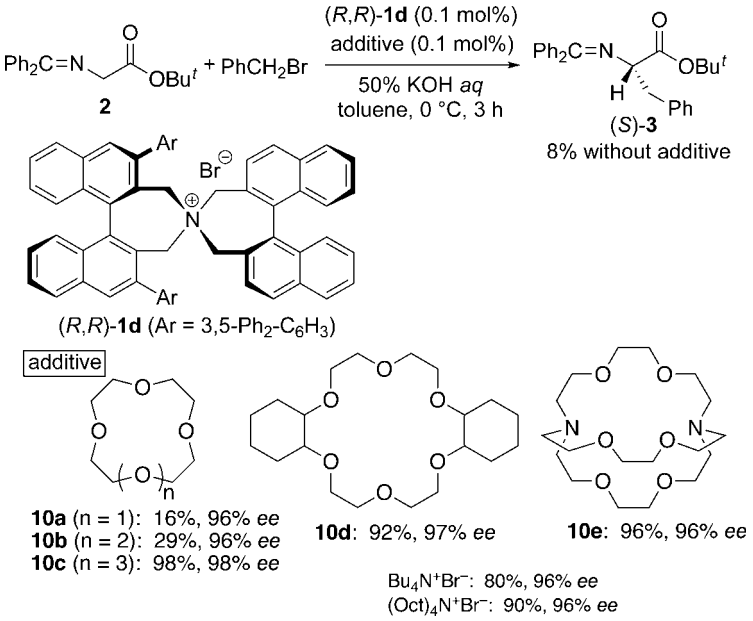


Scheme 5.4

In order to fully induce the potential catalytic activity of *N*-spiro chiral ammonium salts such as **1d**, Maruoka and coworkers have developed binary phase-transfer catalysis using an appropriate achiral co-catalyst [11]. Considering the highly lipophilic nature of **1**, the reaction would proceed through the interfacial mechanism initiated by the direct interfacial deprotonation of **2** with an alkaline metal hydroxide such as potassium hydroxide. Based on this plausible mechanistic profile, it was envisioned that the addition of an achiral co-catalyst which is capable of extracting KOH into the organic phase would substantially accelerate the otherwise slow deprotonation process; this should result in a significant rate enhancement, without diminishing the enantioselectivity if the subsequent enolate exchange with **1** were to be extremely fast. Verification of this hypothesis is illustrated by the realization of novel binary phase-transfer catalyst systems with chiral phase-transfer catalyst **1** and crown ether **10** as an ideal achiral co-catalyst, taking advantage of its well-known ability to extract metal cations (Scheme 5.6). For example, the phase-transfer-catalyzed alkylation of **2** with benzyl bromide under the influence of **1d** (0.1 mol %) was seen to be sluggish and to provide **3** in only 8% yield (94% *ee*), whereas a similar benzylation of **2** in the presence of 18-crown-6 (**10c**, 0.1 mol%) proceeded smoothly to furnish **3** in 98% yield with 98% *ee* [11]. Indeed, the use of small-sized crown ethers such as 15-crown-5 (**10b**) and 12-crown-4 (**10a**) dramatically lowered the chemical yield of **3**. In contrast, similar-sized crown ethers such as **10d** and **10e** gave



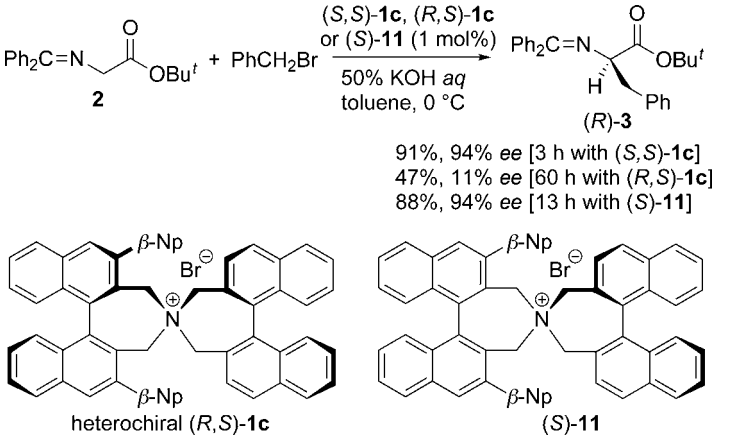
Scheme 5.5



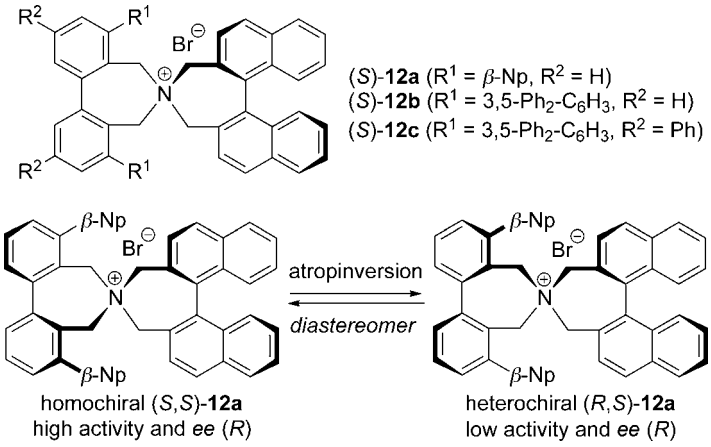
Scheme 5.6

high chemical yields, without losing enantioselectivity. Interestingly, tetrabutyl- and tetraoctylammonium salts also exhibited a similar acceleration effect.

Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of **1** and related catalyst **9**, Maruoka and coworkers have generally used their (*S,S*)- and (*R,R*)-isomers. Surprisingly, however, when the diastereomeric (*R,S*)-**1c** was used for asymmetric benzylation of **2**, the reaction was found to proceed very slowly, such that even after 60 h the



Scheme 5.7



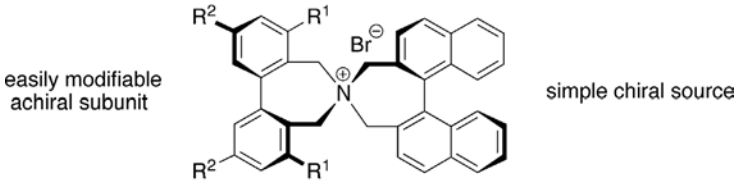
Scheme 5.8

benzylation product (*R*)-**3** was obtained in only 47% yield with very low enantioselectivity. Such a large difference in both reactivity and selectivity between (*S*,*S*)-**1c** and (*R*,*S*)-**1c** prompted the use of a racemic and chiral binaphthyl combination catalyst (*S*)-**11** which gave 88% yield with 94% *ee* after 13 h for a similar asymmetric benzylation reaction (Scheme 5.7).

With this information at hand, Maruoka and coworkers developed a new C_2-symmetric chiral quaternary ammonium bromide **12** which incorporated an achiral, conformationally flexible biphenyl subunit (Scheme 5.8) [12].

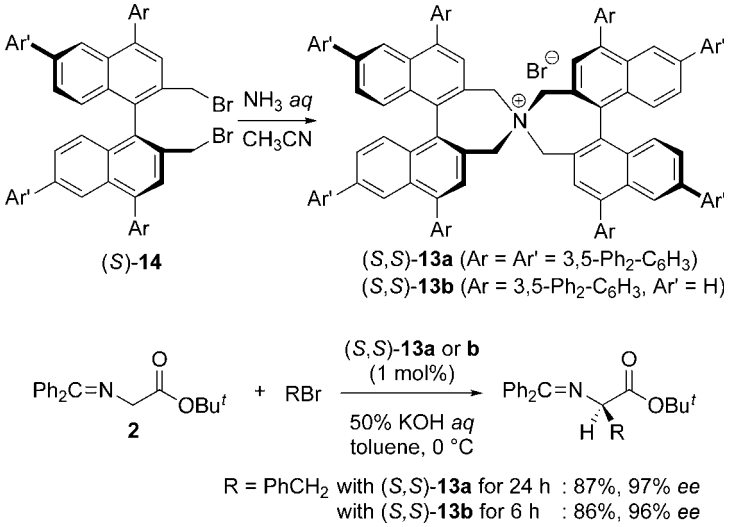
The phase-transfer benzylation of **2** with the catalyst (*S*)-**12a** having β-naphthyl group on the 3,3′-position of the flexible biphenyl moiety proceeded smoothly at 0 °C to afford the corresponding alkylation product (*R*)-**3** in 85% yield with 87% *ee* after 18 h. The origin of the observed chiral efficiency could be ascribed to the considerable difference in catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral (*S*,*S*)-**12a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce **3** with high enantiomeric excess, whereas the heterochiral (*R*,*S*)-**12a** displays low reactivity and stereoselectivity.

This unique phenomenon provides a powerful strategy in the molecular design of chiral catalysts; that is, the requisite chirality can be served by the simple binaphthyl moiety, while an additional structural requirement for fine-tuning of reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure. This certainly obviates the use of two chiral units, and should be appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. Actually, quaternary ammonium bromide possessing a sterically demanding substituent such as (*S*)-**12b** can be easily prepared, and benzylation with (*S*)-**12b** as catalyst gave **9** in 95% yield with 92% ee. Further, the enantioselectivity was enhanced to 95% *ee* with (*S*)-**12c** as a catalyst [12].

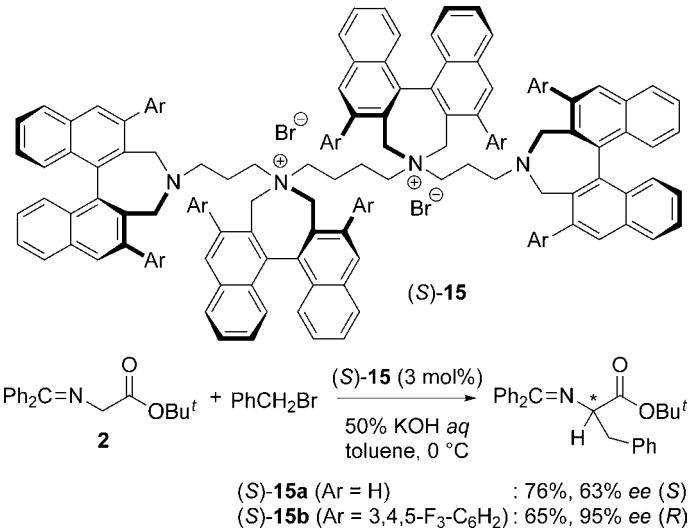


On the other hand, Maruoka and coworkers were intrigued with the preparation of symmetrical *N*-spiro-type catalysts to avoid the independent synthesis of two different binaphthyl-modified subunits required for **1**. Along this line, 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide (*S,S*)-**13** was assembled through the reaction of aqueous ammonia with bis-bromide (*S*)-**14** on the basis of previous studies on the substituent effect of this type of salt. The evaluation of (*S,S*)-**13** as a chiral phase-transfer catalyst in the alkylation of **2** uncovered its high catalytic and chiral efficiency (Scheme 5.9) [9].

The Maruoka group's further efforts toward simplification of the catalyst have led to the design of new, polyamine-based chiral phase-transfer catalysts of type **15**, with expectation of the multiplier effect of chiral auxiliaries, as illustrated in Scheme 5.10 [13]. The chiral efficiency of such polyamine-based chiral phase-transfer catalysts (*S*)-**15** was examined by carrying out an asymmetric alkylation of glycine derivative **2** under phase-transfer conditions. Among various commercially available polyamines, spermidine- and spermine-based polyammonium salts were found to show moderate enantioselectivity. In particular, the introduction of a 3,4,5-trifluorophenyl group at the 3,3′-positions of chiral binaphthyl moieties showed excellent asymmetric induction.

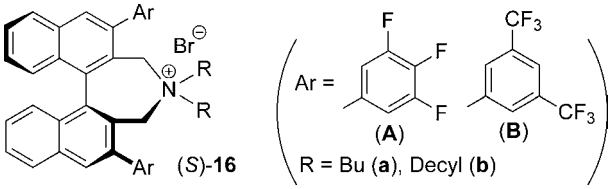


Scheme 5.9



Scheme 5.10

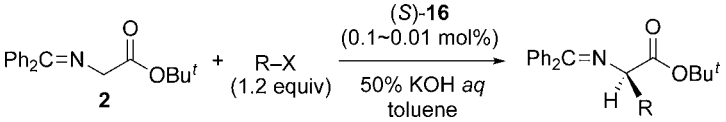
This finding led to the discovery that the chiral quaternary ammonium bromide of type **16**, possessing flexible straight-chain alkyl groups instead of a rigid binaphthyl moiety, functions as an unusually active chiral phase-transfer catalyst [14]. Accordingly, the chemical behavior of the simplified phase-transfer catalysts (*S*)-**16Aa**, (*S*)-**16Ab**, (*S*)-**16Ba** and (*S*)-**16Bb** was examined by carrying out asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2**. Quite surprisingly, these types of catalyst were found to be by far the most active among existing chiral phase transfer catalysts. Indeed, an asymmetric reaction of **2** with benzyl bromide (1.2 equiv.) and 50% aqueous KOH in toluene was effected in the presence of only 0.01 ∼ 0.1 mol% of chiral catalyst (*S*)-**16Aa** under an argon atmosphere at 0 °C for 2∼12 h to furnish the benzylation product (*R*)-**3** almost quantitatively, with excellent enantioselectivity (98∼99% *ee*) (Table 5.2, entries 1–3). A similar tendency was also observed in the case of catalyst (*S*)-**16Ab** (entries 4 and 5).



Other selected examples are also listed in Table 5.2 [14]. Several characteristic features of the present alkylations include:

- In contrast to the existing chiral phase-transfer catalysts, (*S*)-**16Aa**, (*S*)-**16Ab**, (*S*)-**16Ba** and (*S*)-**16Bb** exhibited a high catalytic performance (0.05∼0.1 mol%), demonstrating remarkable efficiency and practicability of the present approach for the enantioselective synthesis of various α-alkyl-α-amino acids.

Table 5.2 Catalytic enantioselective phase-transfer alkylation of glycine derivative **2** catalyzed by (*S*)-**16Aa**, (*S*)-**16Ab**, (*S*)-**16Ba**, and (*S*)-**16Bb**.



Entry	Catalyst (mol%)	RX	Conditions (°C, h)	Yield (%)[b]	*ee* (%) (config.)
1	(*S*)-**16Aa** (0.1)	$PhCH_2Br$	0, 12	99	99 (*R*)
2	(*S*)-**16Aa** (0.05)		0, 2	98	99 (*R*)
3	(*S*)-**16Aa** (0.01)		0, 9	92	98 (*R*)
4	(*S*)-**16Ab** (0.05)		0, 4	94	99 (*R*)
5	(*S*)-**16Ab** (0.01)		0, 24	79	98 (*R*)
6	(*S*)-**16Ba** (0.1)		0, 4	89	91 (*R*)
7	(*S*)-**16Ba** (0.05)		0, 5	87	91 (*R*)
8	(*S*)-**16Ba** (0.01)		0, 48	9	90 (*R*)
9	(*S*)-**16Bb** (0.05)		0, 48	85	93 (*R*)
10	(*S*)-**16Aa** (0.05)	*p*-Me-$PhCH_2Br$	0, 4	99	98 (*R*)
11	(*S*)-**16Aa** (0.05)	*p*-F-$PhCH_2Br$	0, 5	99	98 (*R*)
12	(*S*)-**16Aa** (0.05)	$CH_2{=}CHCH_2Br$	0, 3	87	98 (*R*)
13	(*S*)-**16Aa** (0.01)		0, 48	62	82 (*R*)
14	(*S*)-**16Ab** (0.05)		0, 5	99	97 (*R*)
15	(*S*)-**16Ba** (0.01)		0, 48	60	83 (*R*)
16	(*S*)-**16Bb** (0.05)		0, 48	59	91 (*R*)
17	(*S*)-**16Aa** (0.05)	$HC{\equiv}CCH_2Br$	0, 4	88	98 (*R*)
18	(*S*)-**16Aa** (0.01)		0, 48	26	88 (*R*)
19	(*S*)-**16Ba** (0.05)		0, 46	80	88 (*R*)
20	(*S*)-**16Aa** (0.05)	CH_3CH_2I[a]	0, 72	12	91 (*R*)
21	(*S*)-**16Aa** (0.05)	CH_3CH_2I[a),b]	−20, 1	67	99 (*R*)

[a] Use of 5 equiv. alkyl halide.
[b] Use of $CsOH{\cdot}H_2O$ as base.

- By using $CsOH{\cdot}H_2O$ in place of 50% KOH, the asymmetric alkylation of **2** with a simple alkyl halide such as ethyl iodide proceeded smoothly at −20 °C to furnish the corresponding α-alkyl-α-amino acids in good yield, with high enantioselectivity Table 5.2, entries 20 and 21).

With bis(3,4,5-trifluorophenyl)-substituted catalyst (*S*)-**16A**, the substituent effect of R was examined by changing the number of straight alkyl chains (Figure 5.1). In the asymmetric benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2**, use of $(CH_3(CH_2)_{n\text{-}1})_2NH$ ($n \geq 4$) gave a uniformly high asymmetric induction.

Recently, Maruoka and coworkers have expressed interest in the development of C_2-symmetric phase-transfer catalysts which consist of two chiral biphenyl units, as a new, easily modifiable subunit for further elaboration. To this end, chiral phase-

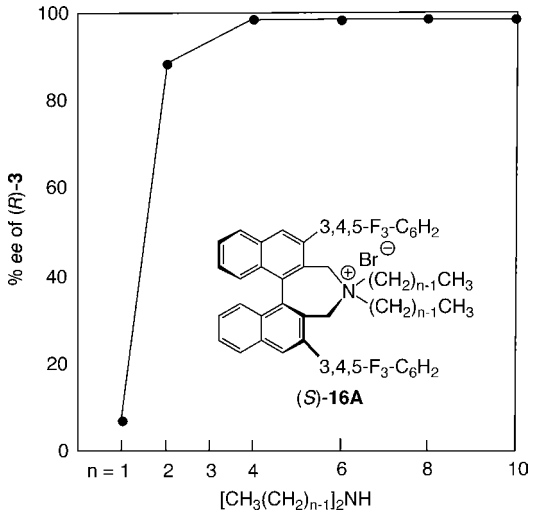
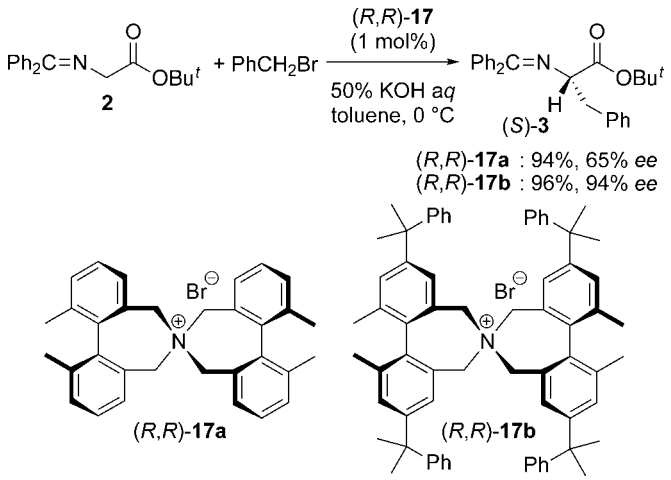


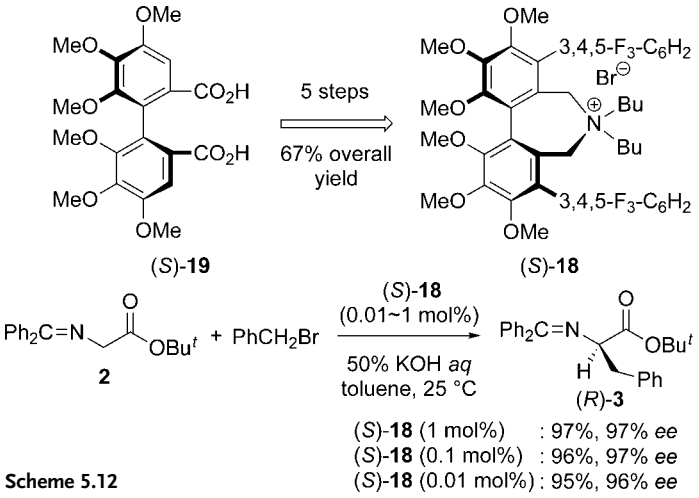
Figure 5.1 Effect of the number of straight alkyl chains in (*S*)-**16A** on enantioselectivity in the asymmetric benzylation of **2**.

transfer catalyst **17** was synthesized and evaluated in the asymmetric alkylation of glycine Schiff base **2** (Scheme 5.11) [15].

In designing practical phase-transfer catalysts, the ready availability of starting chiral sources is crucial. Accordingly, a highly practical, chiral phase-transfer catalyst (*S*)-**18** was conveniently prepared from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid (*S*)-**19** derived from Gallic acid. The catalyst (*S*)-**18** exhibited a high catalytic performance (0.01∼1 mol%) in the asymmetric alkylation of **2** compared to the existing chiral phase-transfer catalysts, thereby providing



Scheme 5.11

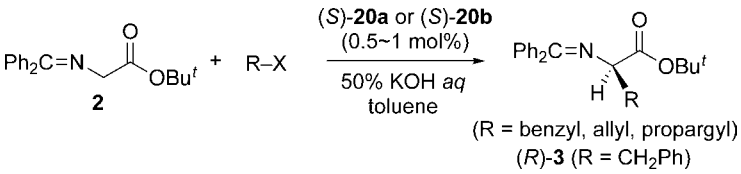


Scheme 5.12

a general and useful procedure for a highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids (Scheme 5.12) [16].

In a similar manner, other chiral phase-transfer catalysts (*S*)-**20a** and (*S*)-**20b** were conveniently prepared in five steps from the known (*S*)-6,6′-dimethylbiphenyl-2,2′-diol (*S*)-**21** (>99% ee), which is conveniently derived from commercially available

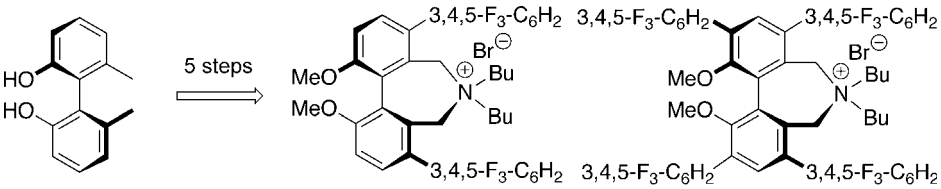
Table 5.3 Catalytic enantioselective phase-transfer alkylation of glycine derivative **2**.



Entry	Catalyst (mol%)	R–X (equiv.)	Conditions (°C, h)	Yield (%)	*ee* (%) (config.)
1	(*S*)-**20a** (1)	$PhCH_2Br$ (3)	0, 5	97	96 (*R*)
2	(*S*)-**20a** (1)	$PhCH_2Br$ (3)	r.t., 3	99	91 (*R*)
3	(*S*)-**20a** (1)	$CH_2{=}CHCH_2Br$ (3)	0, 2.5	90	93 (*R*)
4	(*S*)-**20a** (1)	$CH{\equiv}CCH_2Br$ (3)	0, 4	95	86 (*R*)
5	(*S*)-**20b** (1)	$PhCH_2Br$ (1.5)	0, 4	94	86 (*R*)
6	(*S*)-**20b** (1)	$PhCH_2Br$ (1.5)	r.t., 2.5	96	98 (*R*)
7	(*S*)-**20b** (1)	$CH{\equiv}CCH_2Br$ (1.5)	0, 3	94	87 (*R*)
8	(*S*)-**20b** (1)	$CH_2{=}CHCH_2Br$ (1.5)	0, 3.5	92	88 (*R*)
9	(*S*)-**20b** (0.5)	$CH{\equiv}CCH_2Br$ (2)	20, 6	92	91 (*R*)
10	(*S*)-**20b** (0.5)	$CH_2{=}CHCH_2Br$ (1.5)	20, 5	90	93 (*R*)
11	(*S*)-**20b** (0.5)	$PhCH_2Br$ (1.2)	20, 5	93	95 (*R*)

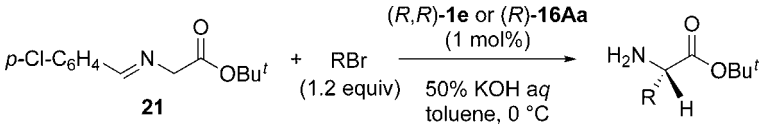
r.t. = room temperature.

4,6-di-*tert*-butyl-*m*-cresol [17]. The chiral efficiency of (*S*)-**20a** and (*S*)-**20b** was evaluated by carrying out an asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2**, as shown in Table 5.3. Thus, reaction of **2** with benzyl bromide (3 equiv.) and 50% aqueous KOH in toluene was effected in the presence of 1 mol% of catalyst (*S*)-**20a** under an argon atmosphere to furnish the benzylation product (*R*)-**3** in 97% yield with excellent enantioselectivity (96% ee) (Table 5.3, entry 1). As expected, the enantioselectivity was decreased upon warming to room temperature (entry 2). Asymmetric allylation and propargylation also proceeded smoothly at 0 °C, with high enantioselectivity (entries 3 and 4). Based on these results, the asymmetric benzylation of **2** with catalyst (*S*)-**20b** was carried out both at 0 °C and at room temperature (entries 5 and 6). Surprisingly, the room-temperature reaction was found to exhibit a higher enantioselectivity. This unique temperature-related effect on enantioselectivity was also observed in asymmetric propargylation and allylation reactions (entries 7 and 8 versus 9 and 10). The catalytic amount of (*S*)-**20b** can be reduced to 0.5 mol% (entries 9∼11).



The enantioselective alkylation of glycine Schiff base **2** using chiral phase-transfer catalysts has been developed into a powerful method for the synthesis of optically active α-amino acid derivatives [2]. A key feature of this extremely useful asymmetric transformation is the selective monoalkylation of **2** due to the considerable difference in acidity of the α-proton between the starting substrate **2** and the corresponding monoalkylation product **3**. This property, which is imparted by the presence of the benzophenone imine moiety, is essential for securing the configurational stability of the newly created stereogenic center in **3** under the basic reaction conditions. On the other hand, the *p*-chlorobenzaldehyde imine of α-alkyl-α-amino acid *tert*-butyl ester has been employed in the preparation of optically active α,α-dialkyl-α-amino acid derivatives by phase-transfer-catalyzed alkylation [18,19]. This is certainly because the α-proton of such an imine is sufficiently acidic to be deprotonated under typical conditions, in contrast to its benzophenone imine counterpart **2**; consequently, aldimine Schiff base **21**, derived from glycine *tert*-butyl ester, has long been regarded as an unsuitable substrate for the stereoselective monoalkylation. Recently, Maruoka and coworkers found that the selective monoalkylation of **21** is indeed feasible under mild liquid–liquid phase-transfer conditions, and that the binaphthyl-derived chiral quaternary ammonium bromides (*R,R*)-**1e** and (*R*)-**16Aa** act as efficient catalysts to achieve rigorous stereochemical control (Scheme 5.13) [20].

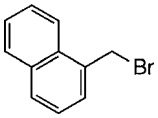
The requisite aldimine Schiff base **21** can be readily prepared by the simple imine formation between glycine *tert*-butyl ester and *p*-chlorobenzaldehyde in MeOH at room temperature, with the aid of $MgSO_4$. The asymmetric monoalkylation of **21** was



Scheme 5.13

then performed by introducing a 50% KOH aqueous solution into a mixture of **21**, benzyl bromide and (*R,R*)-**1e** (or (*R*)-**16Aa**) in toluene at 0 °C under an argon atmosphere, followed by a vigorous stirring at that temperature. The selected examples listed in Table 5.4 demonstrate the rather surprising utility of this method. Generally, 1 mol% of (*R,R*)-**1e** or (*R*)-**16Aa** with 1.2 equiv. of alkyl halide was sufficient for the smooth reaction. In addition to the representative *p*-substituted benzylic bromides, 1-bromomethyl naphthalene was well accommodated, offering practical access to a wide range of optically pure phenyalanine analogues (Table 5.4, entries 3–8). For the simple allylation, **16Aa** appeared to be a suitable catalyst (entries 9 and 10), while higher asymmetric induction was attained with **1e** when cinnamyl bromide was a reacting partner (entries 13 and 14). Although a significant rate retardation seemed inevitable in the reaction with less-reactive alkyl halides (e.g., ethyl iodide) under the present conditions (entry 15), this was overcome by using an excess amount of the electrophile (entries 16–17).

Table 5.4 Asymmetric monoalkylation of **21** under phase-transfer conditions catalyzed by chiral quaternary ammonium bromide (*R,R*)-**1e** or (*R*)-**16Aa**.

Entry	Alkyl halide (R^1X)	Catalyst	Time (h)	Yield (%)	*ee* (%) (config.)
1	$PhCH_2Br$	(*R,R*)-**1e**	2	99	99 (*S*)
2		(*R*)-**16Aa**	2	95	98 (*S*)
3	*p*-Me-$C_6H_4CH_2Br$	(*R,R*)-**1e**	2	97	99
4		(*R*)-**16Aa**	4.5	96	98
5	*p*-F-$C_6H_4CH_2Br$	(*R,R*)-**1e**	2	99	95
6		(*R*)-**16Aa**	1.5	97	99
7		(*R,R*)-**1e**	2	96	99
8		(*R*)-**16Aa**	2	96	98
9	$CH_2{=}CHCH_2Br$	(*R,R*)-**1e**	2	84	92
10		(*R*)-**16Aa**	2	92	98
11	$CH_2{=}C(Me)CH_2Br$	(*R,R*)-**1e**	2	99	98
12		(*R*)-**16Aa**	2	95	96
13	*trans*-$PhCH{=}CHCH_2Br$	(*R,R*)-**1e**	3	82	94
14		(*R*)-**16Aa**	6	90	90
15	EtI	(*R,R*)-**1e**	10	43	97
16[a)]		(*R,R*)-**1e**	5	93	99
17[a)]		(*R*)-**16Aa**	6	81	90

[a)] With 10 equiv. of EtI.

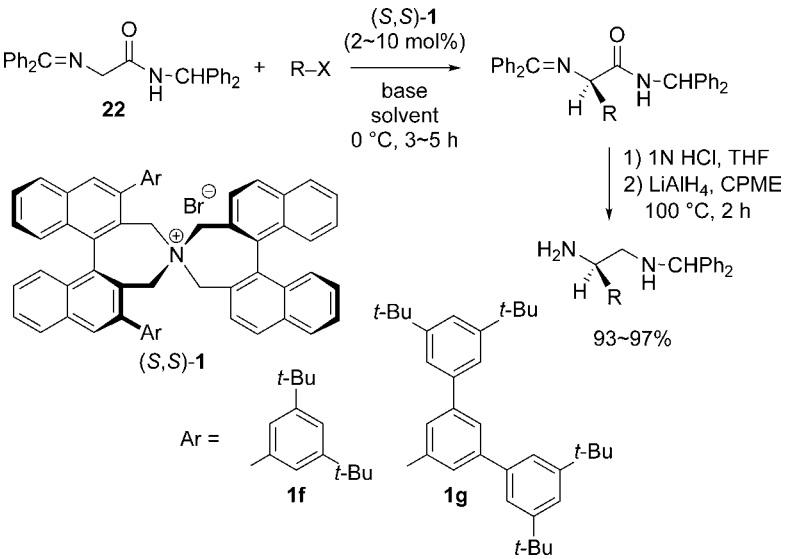
Table 5.5 Asymmetric phase-transfer alkylation of glycine amide Schiff base **22**.

Entry	Alkyl halide (R–X) (equiv.)	Catalyst (mol%)	Base	Solvent	Yield (%)	*ee* (%) (config.)
1	$PhCH_2Br$	(*S*,*S*)-**1f** (2)	50% KOH	Toluene	95	39 (*R*)
2		(*S*,*S*)-**1g** (2)			98	92 (*R*)
3	$CH_2{=}CHCH_2Br$				99	98 (*R*)
4	BuI		sat. CsOH		94	97 (*R*)
5	Cyclohexylmethyl iodide				82	98 (*R*)
6	*i*-PrI				82	82 (*R*)
7				Mesitylene	81	90 (*R*)
8		(*S*,*S*)-**1g** (5)			90	90 (*R*)
9	Cyclopentyl iodide	(*S*,*S*)-**1g** (2)			91	96
10	Cyclohexyl iodide	(*S*,*S*)-**1g** (10)			71	95
11	Cycloheptyl iodide	(*S*,*S*)-**1g** (10)			80	89

5.2.1.2 Asymmetric Monoalkylation of Glycine Amide Schiff Bases

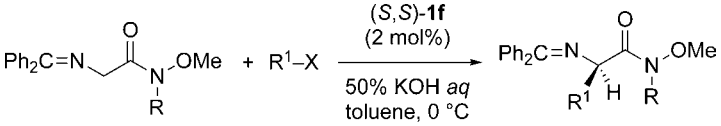
As a prochiral glycine-derived Schiff base, not only esters but also amides can be used as suitable substrates for asymmetric alkylation under phase-transfer conditions.

By using glycine diphenylmethyl (Dpm) amide-derived Schiff base **22** as a key substrate and *N*-spiro chiral quaternary ammonium bromide **1g** as an ideal catalyst, a high enantioselectivity was achieved, even in the alkylation with less-reactive simple secondary alkyl halides, as shown in Table 5.5 [21]. This system offers a facile access to structurally diverse optically active vicinal diamines in combination with the subsequent reduction (Scheme 5.14) [21].



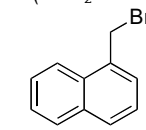
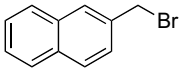
Scheme 5.14

Table 5.6 Asymmetric phase-transfer alkylation of protected glycine weinreb amides **23**.



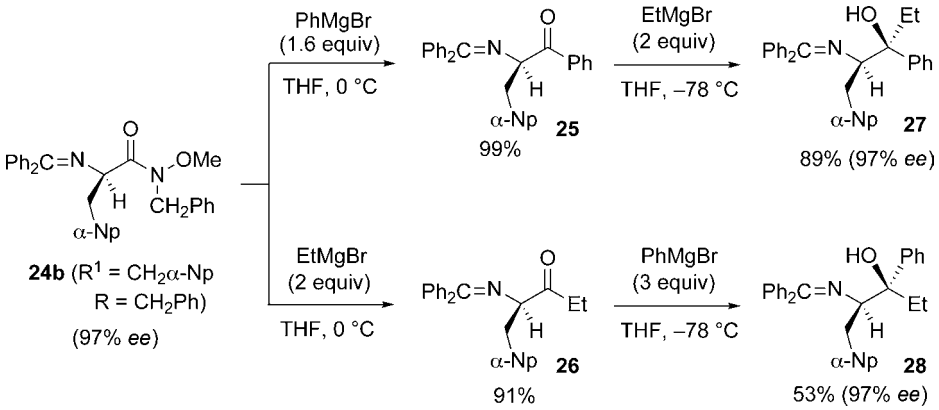
23a (R = Me)
23b (R = CH_2Ph)

24a (R = Me)
24b (R = CH_2Ph)

Entry	Alkyl halide (R^1X)	Substrate (R)	Time (h)	Yield (%)	*ee* (%) (config.)
1	CH_2=$CHCH_2Br$	Me	6	96	96 (*R*)
2[a)]			3	83	79 (*R*)
3		CH_2Ph	6	99	97 (*R*)
4	CH_2=$C(Me)CH_2Br$		6	99	97 (*R*)
5	$CH(CCH_2Br$		6	92	96 (*R*)
6			6	98	97 (*R*)
7			6	99	91 (*R*)
8	EtI		8	97	94 (*R*)
9	BuI		8	77	92 (*R*)

[a)] With (*S*,*S*)-**1g** as catalyst.

Furthermore, this approach was found to be successfully applicable to the asymmetric alkylation of Weinreb amide derivative **23** utilizing **1f** as a catalyst. These selected results are summarized in Table 5.6. Optically active α-(α-$NpCH_2$)-α-amino acid Weinreb amide **24b** ($R^1 = CH_2$α-Np; R = CH_2Ph) can be efficiently



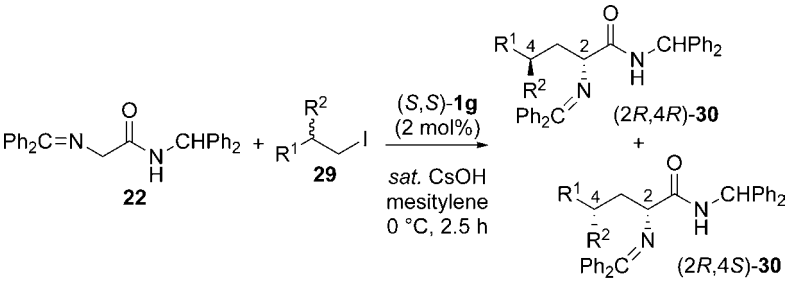
Scheme 5.15

converted to the corresponding amino ketones **25** and **26** by simple treatment with Grignard reagents. In addition, alkylation of the optically active α-amino ketones **25** and **26** into both *syn* and *anti* α-amino alcohols **27** and **28** with almost complete relative and absolute stereochemical control have been achieved (Scheme 5.15) [22].

5.2.1.3 Diastereoselective Alkylation of Glycine Schiff Base with Optically Enriched Alkyl Halides

Despite numerous efforts to develop the asymmetric phase-transfer-catalyzed alkylation of **2** into a powerful method for the synthesis of natural and unnatural α-amino acids, the stereochemistry of the alkylation of **2** with chiral electrophiles has scarcely been addressed.

With regards to studies on the stereoselective functionalization of prochiral glycine Dpm amide derivative **22**, Maruoka and coworkers found that chiral ammonium enolate generated from **1g** and **22** had an ability to recognize the chirality of β-branched primary alkyl halides, which provides impressive levels of kinetic resolution during the alkylation with racemic halide **29**, allowing for two α- and γ-stereocenters of **30** to be controlled, as exemplified in Scheme 5.16 [22].



R^1 = Ph, R^2 = Me : 89%, dr = 91 (99% *ee*):9 (93% *ee*)
R^1 = *c*-Hex, R^2 = Me : 93%, dr = 93 (97% *ee*):7 (90% *ee*)

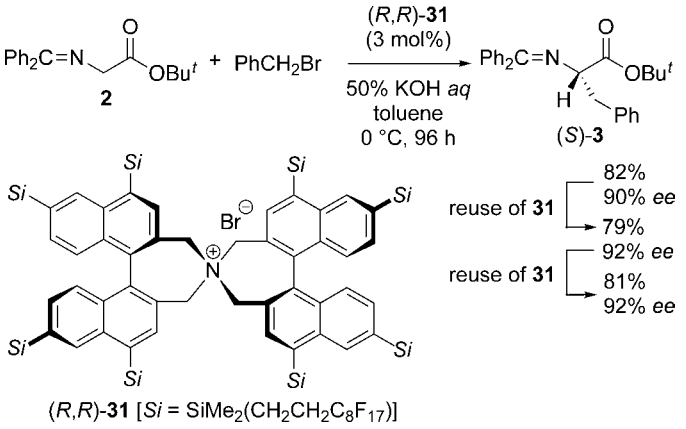
Scheme 5.16

5.2.1.4 Recyclable Catalysts and Reagents and Solid-Phase Synthesis

The enantioselective synthesis of α-amino acids employing easily available and reusable chiral catalysts or reagents presents clear advantages for large-scale applications. Accordingly, recyclable fluorous chiral phase-transfer catalyst **31** has been developed by the authors' group, and its high chiral efficiency and reusability demonstrated in the asymmetric alkylation of **2**. After the reaction, **31** could be easily recovered by simple extraction with FC-72 (perfluorohexanes) as a fluorous solvent and used for the next run, without any loss of reactivity and selectivity (Scheme 5.17) [23].

5.2.1.5 Application of Asymmetric Synthesis of α-Amino Acids

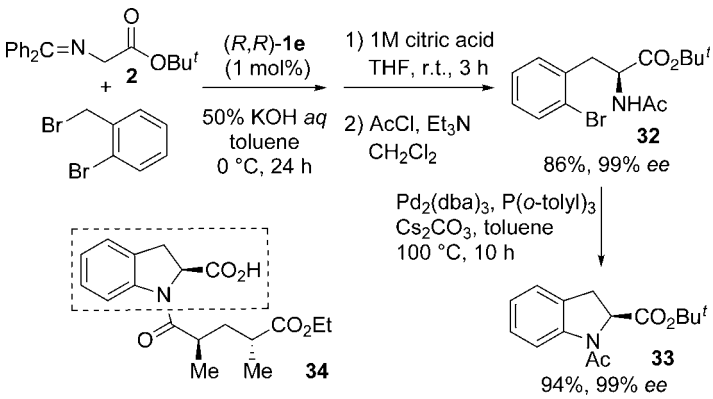
The vast synthetic utility of the asymmetric phase-transfer alkylation of glycine Schiff base **2** has been realized by its successful application to the synthesis of various useful amino acid derivatives and natural products.



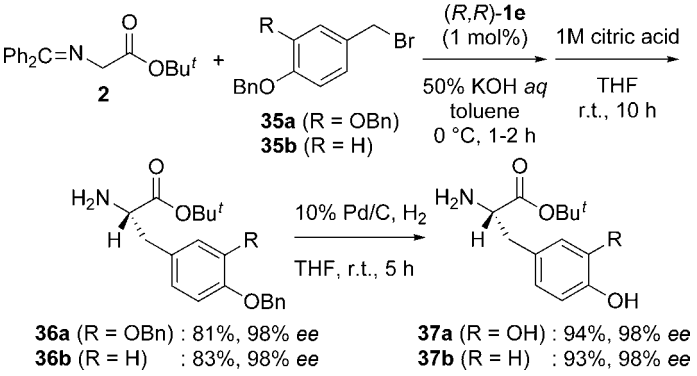
Scheme 5.17

With both enantiomers of **1e** in hand, the asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate **33** was carried out, this being a key intermediate in the synthesis of the angiotensin-converting enzyme (ACE) inhibitor **34** (Scheme 5.18) [7e]. The structure and stereochemical integrity of **33** was simultaneously constructed by the asymmetric alkylation of **2** with *o*-bromobenzyl bromide in the presence of (*R,R*)-**1e**, and subsequent hydrolysis and *N*-acetylation afforded **32** in 86% yield with 99% *ee*. According to the Buchwald procedure, almost enantiopure **32** was efficiently converted to **33** (94%, 99% *ee*) [7e].

The chiral phase-transfer catalysis of **1e** was further applied to the facile synthesis of L-Dopa ester and its analogue, which usually have been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes, and tested as potential drugs for the treatment of Parkinson's disease. Phase-transfer-catalyzed alkylation of **2** with the requisite benzyl bromide **35a** in toluene-50% KOH aqueous solution proceeded smoothly at 0 °C under the influence of (*R,R*)-**1e** to furnish fully protected L-Dopa *tert*-butyl ester; this was subsequently hydrolyzed to afford the corresponding amino ester **36a** in 81% yield with 98% *ee*. Debenzylation of **36a** under



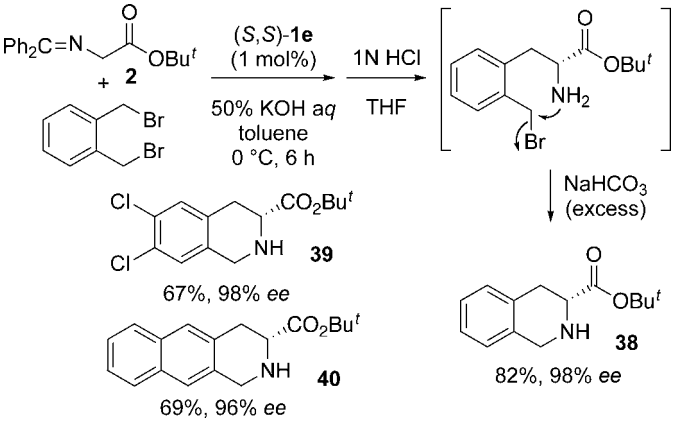
Scheme 5.18



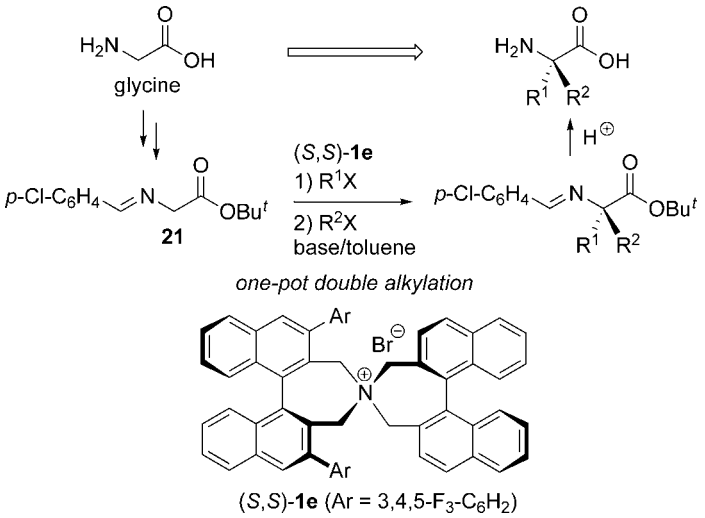
Scheme 5.19

catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester **37a** in 94% yield. The successful asymmetric synthesis of the natural tyrosine *tert*-butyl ester **37b** in similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues (Scheme 5.19) [7e,24].

The catalytic and chiral efficiency of (*S,S*)-**1e** was also appreciated in the asymmetric synthesis of isoquinoline derivatives, which are important conformationally constrained α-amino acids. Treatment of **2** with α,α′-dibromo-*o*-xylene under liquid–liquid phase-transfer conditions in the presence of (*S,S*)-**1e** showed complete consumption of the starting Schiff base. Imine hydrolysis and subsequent treatment with an excess amount of $NaHCO_3$ facilitated intramolecular ring closure to give 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butyl ester **38** in 82% yield with 98% *ee*. A variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives possessing different aromatic substituents, such as **39** and **40**, can be conveniently prepared in a similar manner, with excellent enantioselectivity (Scheme 5.20) [25].



Scheme 5.20



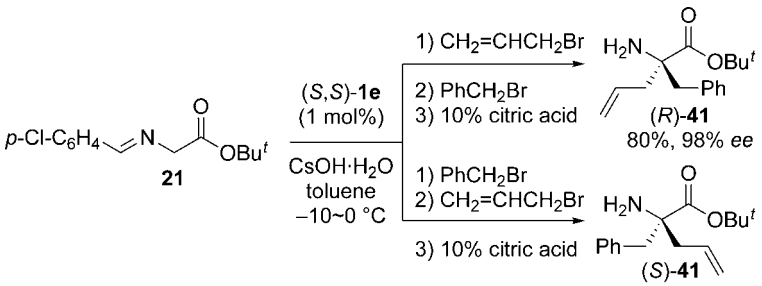
Scheme 5.21

5.2.2
Asymmetric Synthesis of α,α-Dialkyl-α-Amino Acids

Non-proteinogenic, chiral α,α-dialkyl-α-amino acids possessing stereochemically stable quaternary carbon centers have been significant synthetic targets, not only because they are often effective enzyme inhibitors but also because they are indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation [26], and in this respect phase-transfer catalysis has made unique contributions.

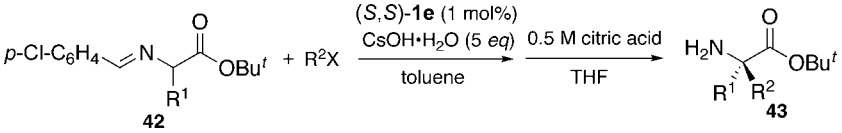
Since the aldimine Schiff base **21** can be readily prepared from glycine, direct stereoselective introduction of two different side chains to **21** by appropriate chiral phase-transfer catalysis would provide an attractive, yet powerful, strategy for the asymmetric synthesis of structurally diverse α,α-dialkyl-α-amino acids. This possibility of a one-pot asymmetric double alkylation has been realized by using *N*-spiro chiral quaternary ammonium bromide **1e** (Scheme 5.21).

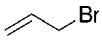
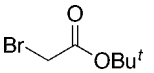
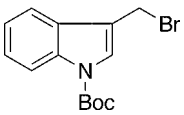
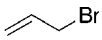
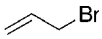
The initial treatment of a toluene solution of **21** and (*S,S*)-**1e** (1 mol%) with allyl bromide (1 equiv.) and $CsOH \cdot H_2O$ at −10 °C, and subsequent reaction with benzyl



Scheme 5.22

Table 5.7 Catalytic enantioselective synthesis of α,α-dialkyl-α-amino acids by phase-transfer alkylation.

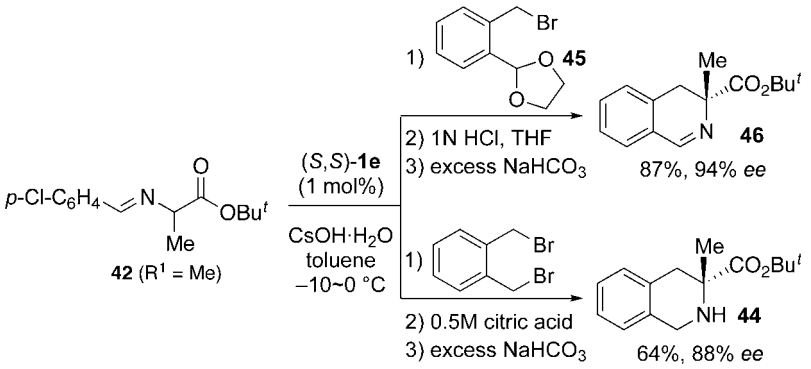


Entry	42 (R^1)	R^2X	Conditions (°C, h)	Yield (%)	*ee* (%) (config.)
1	Me	$PhCH_2Br$	0, 0.5	85	98 (*R*)
2			0, 0.5	73	98 (*R*)
3		EtI	0, 0.3	71	99 (*R*)
4			−20, 2	60	93 (*R*)
5			−10, 0.7	78	91 (*R*)
6	$PhCH_2$		0, 0.5	71	97 (*S*)
7	*i*-Bu	$PhCH_2Br$	0, 0.5	64	92
8			0, 1	70	93

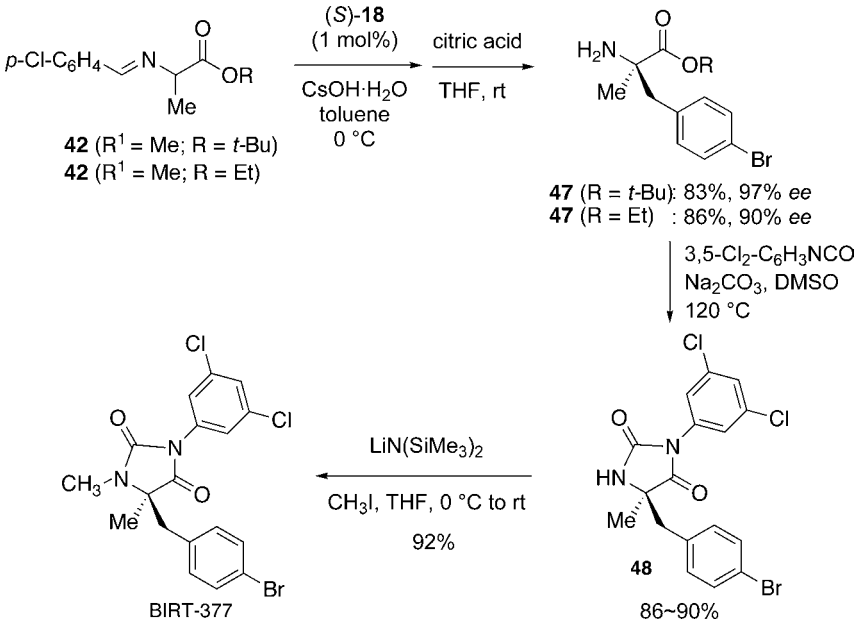
bromide (1.2 equiv.) at 0 °C, resulted in formation of the double alkylation product (*R*)-**41** in 80% yield with 98% *ee* after hydrolysis. Notably, in the double alkylation of **21** by the addition of halides in reverse order, the absolute configuration of the product (*S*)-**41** was confirmed as being opposite (Scheme 5.22) [19].

Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldimine Schiff base **42** derived from the corresponding α-amino acids. Indeed, *dl*-alanine-, phenylalanine- and leucine-derived imines **42** (R^1 = Me, CH_2Ph, *i*-Bu) can be alkylated smoothly under similar conditions, affording the desired non-coded amino acid esters **43** with excellent asymmetric induction, as exemplified in Table 5.7 [19].

This powerful quaternization method enabled the catalytic asymmetric synthesis of quaternary isoquinoline derivatives with **42** (R^1 = Me) as a substrate. When **42** (R^1 = Me) was treated with α,α′-dibromo-*o*-xylene, $CsOH{\cdot}H_2O$ and (*S*,*S*)-**1e** (1 mol%) in toluene at 0 °C, the transient monoalkylation product was rapidly produced, and subsequently transformed into the desired **44** (64%, 88% *ee*) during the work-up procedure. Catalytic asymmetric alkylation of **42** (R^1 = Me) with functionalized benzyl bromide **45**, followed by the sequential treatment with 1 M HCl and then excess $NaHCO_3$, furnished the corresponding dihydroisoquinoline derivative **46** in 87% with 94% *ee* (Scheme 5.23) [25].

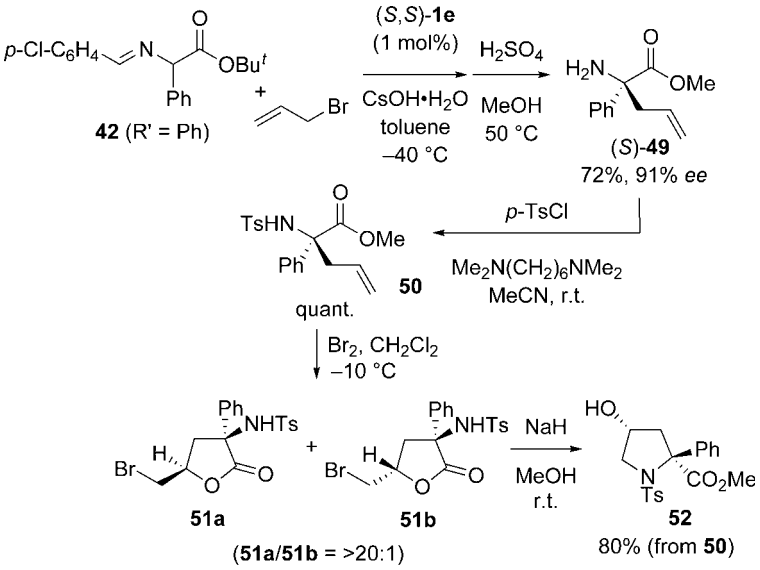


Scheme 5.23



Scheme 5.24

The quaternization method is also highlighted by the short asymmetric synthesis of cell adhesion molecule BIRT-377 (Scheme 5.24), which is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) [16]. Thus, asymmetric *p*-bromobenzylation of the alanine derivative **42** ($R^1 = Me$) with (*S*)-**18** under similar phase-transfer conditions as described above gave rise to *p*-bromobenzylalanine ester **10** in 97% *ee* (83% yield). A similar asymmetric *p*-bromobenzylation of alanine ethyl ester **42** ($R^1 = Me$, R = Et) gave the amino ester **47** (R = Et) in 90% *ee* (86% yield). The amino ester **47** (R = *t*-Bu or Et) was treated with 3,5-dichlorophenyl isocyanate in the presence of sodium carbonate in dimethylsulfoxide (DMSO) to furnish the hydantoin **48** in 86%

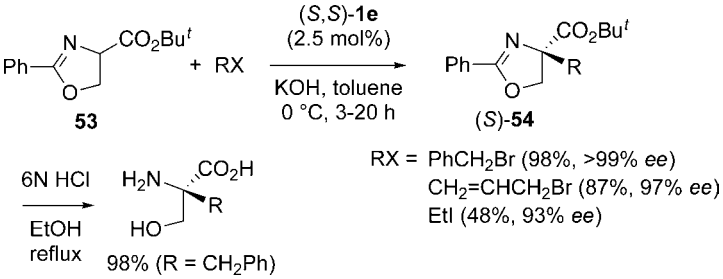


Scheme 5.25

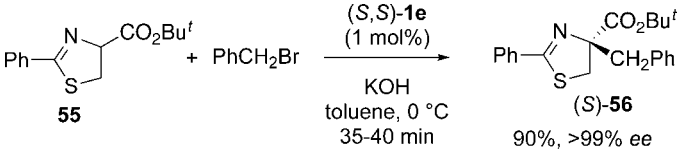
or 90% yield, respectively. *N*-Methylation of **48** was effected with lithium bis (trimethylsilyl)amide and methyl iodide in tetrahydrofuran (THF) to afford BIRT-377 in 92% yield.

Recently, Maeda and coworkers utilized the (*S,S*)-**1e**-catalyzed asymmetric alkylation of phenylglycine-derived Schiff base **42** (R^1 = Ph) for the stereoselective synthesis of a 4-hydroxy-2-phenylproline framework [27]. After hydrolysis and transesterification, the resulting (*S*)-**49** was derivatized to its *N*-tosylate **50**. Subsequent treatment of **50** with Br_2 in CH_2Cl_2 resulted in the formation of γ-lactone **51** with high diastereoselectivity; this was then treated with NaH in methanol to give essentially pure (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative **52** in 80% yield from **50** (Scheme 5.25).

The efficient phase-transfer-catalyzed alkylation strategy with **1e** was successfully applied by Jew and Park to the asymmetric synthesis of α-alkyl serines, using phenyl oxazoline derivative **53** as a requisite substrate [28]. The reaction is general, however, and provides a practical access to a variety of optically active α-alkyl serines through acidic hydrolysis of **54** (Scheme 5.26).



Scheme 5.26

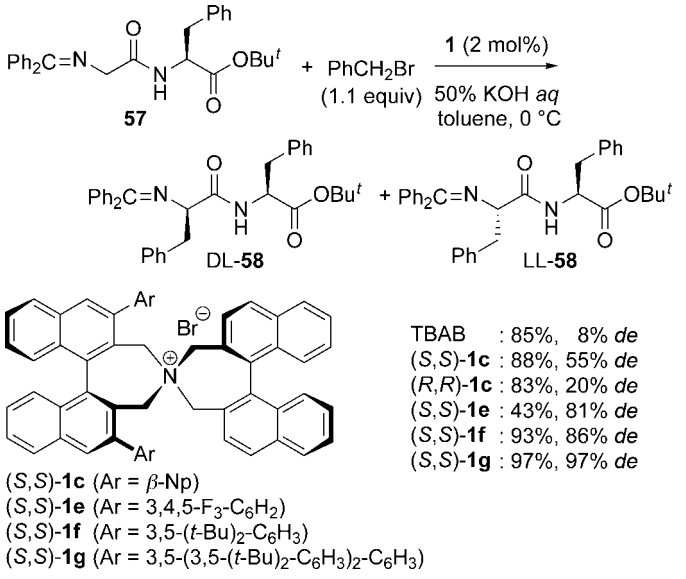


Scheme 5.27

Jew and Park also succeeded in expanding the methodology to the similar asymmetric alkylation of 2-phenyl-2-thiazoline-4-carboxylic acid ester **55** to furnish optically enriched α-alkyl cysteine derivatives **56** (Scheme 5.27) [29].

5.2.3
Alkylation of Schiff Base-Activated Peptides

Peptide modification is an essential, yet flexible, synthetic concept for the efficient target screening and optimization of lead structures in the application of naturally occurring peptides as pharmaceuticals. The introduction of side chains directly to a peptide backbone represents a powerful method for preparing unnatural peptides [30]. In general, the achiral glycine subunit has been used for this purpose, and glycine enolates and radicals, as well as glycine cation equivalents, have been exploited as reactive intermediates. However, control of the stereochemical outcome of these processes in an absolute sense is a difficult task, especially for the modification of linear peptides, and hence the development of an efficient and practical approach to establish sufficient stereoselectivity and general applicability has been an issue of central importance.

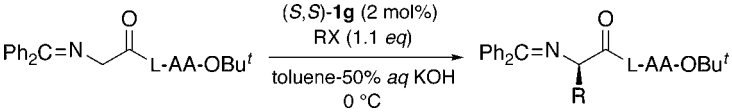


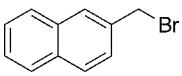
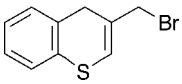
Scheme 5.28

Upon facing the difficulty of stereochemical control in peptide alkylation events, Maruoka and coworkers envisaged that the chiral phase-transfer catalyst should play a crucial role in achieving an efficient chirality transfer, and consequently examined the alkylation of the dipeptide, Gly-L-Phe derivative **57** (Scheme 5.28) [31]. When a mixture of **57** and tetrabutylammonium bromide (TBAB, 2 mol%) in toluene was treated with a 50% KOH aqueous solution and benzyl bromide at 0 °C for 4 h, the corresponding benzylation product **58** was obtained in 85% yield with the diastereomeric ratio (DL-**58**:LL-**58**) of 54:46 (8% *de*). In contrast, the reaction with chiral quaternary ammonium bromide (*S*,*S*)-**1c** under similar conditions gave rise to **58** with 55% *de*. The preferential formation of LL-**58** in lower *de* in the reaction with (*R*,*R*)-**1c** indicated that (*R*,*R*)-**1c** is a mismatched catalyst for this diastereofacial differentiation of **57**. Changing the 3,3′-aromatic substituent (Ar) of the catalyst **1** dramatically increased the stereoselectivity, and almost complete diastereocontrol was realized with (*S*,*S*)-**1g**.

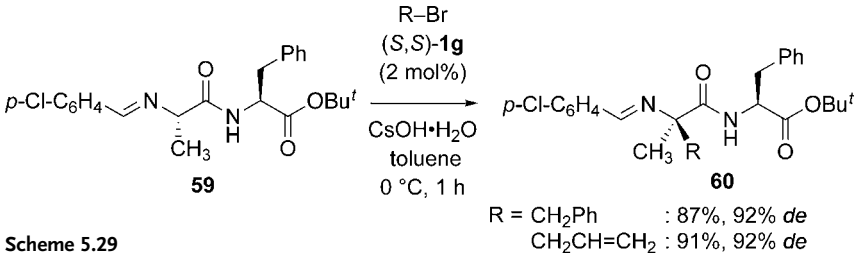
A variety of alkyl halides can be employed as an electrophile in this alkylation, as summarized in Table 5.8 (entries 1–5). The efficiency of the transmission of stereochemical information was not affected by the side-chain structure of the pre-existing amino acid residues, as demonstrated in the phase-transfer benzylation

Table 5.8 Stereoselective *N*-terminal alkylation of dipeptides by chiral phase-transfer catalysis.



Entry	AA	RX	Yield (%)	*de* (%)
1	Phe		89	98
2			80	96
3[a)]		CH_3CH_2I	90	98
4			92	96
5[a)]			95	91
6	Leu	$PhCH_2Br$	91	96
7	Val		85	93
8	Tyr(Bn)		90	98
9	Ala		92	93
10[b)]	Pro		80	90

[a)] Use of sat. CsOH as an aqueous base.
[b)] With (*S*,*S*)-**1f** as catalyst.

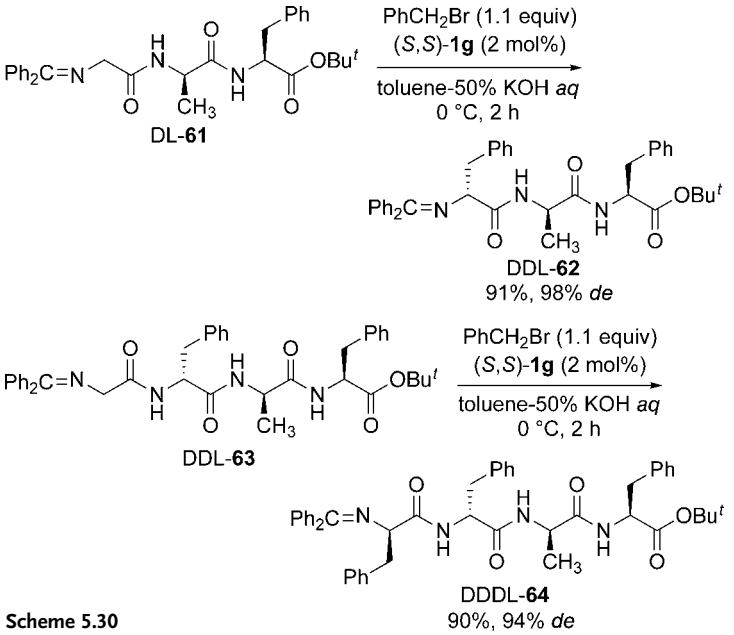


Scheme 5.29

of various dipeptides derived from natural α-amino acids (entries 6–9). Interestingly, sterically less-demanding (*S,S*)-**1f** was found to be a suitable catalyst for the substrate possessing the L-proline *tert*-butyl ester moiety (entry 10).

Further, this method allowed an asymmetric construction of non-coded α,α-dialkyl-α-amino acid residues at the peptide terminal, as exemplified by the stereoselective alkylation of the dipeptide, L-Ala-L-Phe derivative **59** (Scheme 5.29) [31].

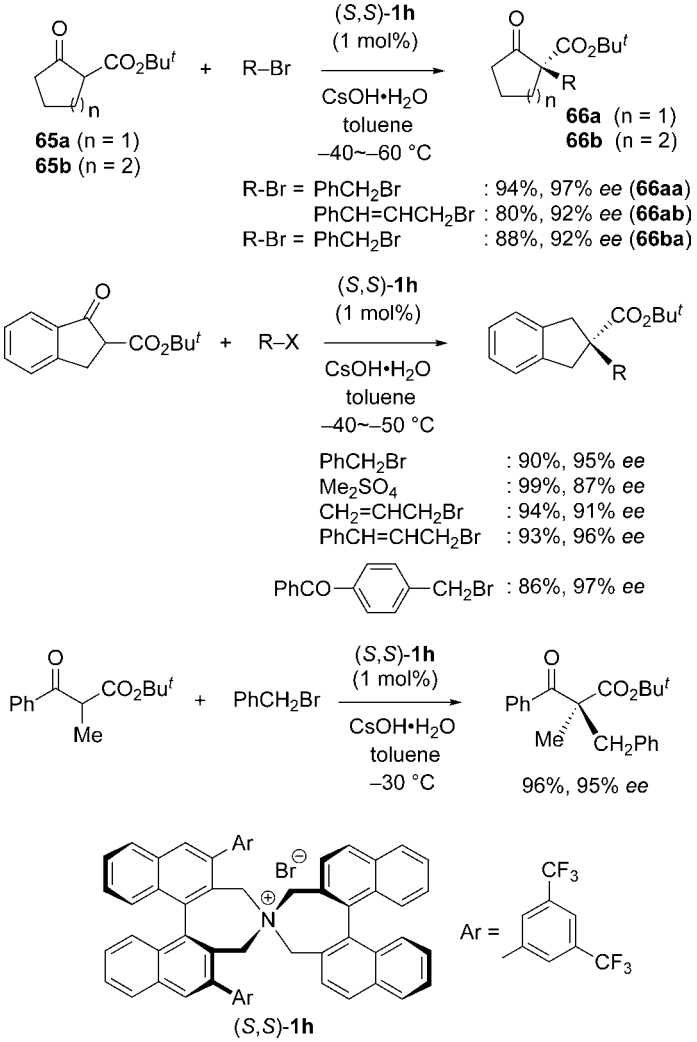
Asymmetric phase-transfer catalysis with (*S,S*)-**1g** can be successfully extended to the stereoselective *N*-terminal alkylation of Gly-Ala-Phe derivative **61** (i.e., the asymmetric synthesis of tripeptides), where (*S,S*)-**1g** turned out to be a matched catalyst in the benzylation of DL-**61**, leading to the almost exclusive formation of DDL-**62**. This tendency for stereochemical communication was consistent in the phase-transfer alkylation of DDL-**63**, and the corresponding protected tetrapeptide DDDL-**64** was obtained in 90% yield with excellent stereochemical control (94% *de*) (Scheme 5.30) [31].



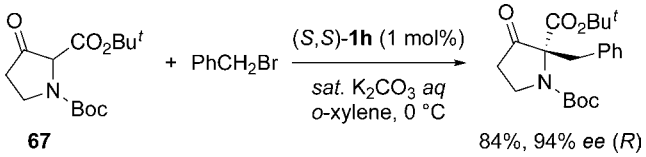
Scheme 5.30

5.2.4
Other Alkylations

Efficient, highly enantioselective construction of quaternary stereocenter on β-keto esters under phase-transfer conditions has been achieved using *N*-spiro chiral quaternary ammonium bromide **1h** as catalyst [32]. This system has a broad generality in terms of the structure of β-keto esters **65** and alkyl halides (Scheme 5.31). The resulting alkylation products **66** can easily be converted into the corresponding β-hydroxy esters and β-amino esters, respectively.



Scheme 5.31



Scheme 5.32

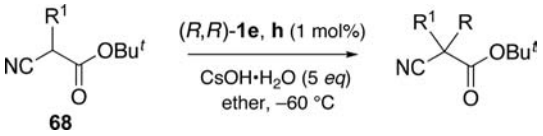
Access to enantioenriched carbonyl compounds of high value which possess quaternary α-carbon stereocenters containing hetero-functionalities represents one of the most challenging tasks in phase-transfer-catalyzed asymmetric alkylation. In due course, Maruoka and coworkers devised the asymmetric alkylation of cyclic α-amino-β-keto esters **67** with C_2-symmetric phase-transfer catalyst **1h** as a means of obtaining aza-cyclic amino acids with quaternary stereocenters (Scheme 5.32) [33].

The highly enantioselective alkylation of α-substituted α-cyanoacetates was achieved using chiral phase-transfer catalysts of type **1e** and **1h** to afford α,α-disubstituted α-cyanoacetates possessing an asymmetric quaternary carbon center with high enantioselectivity, as shown in Table 5.9 [34].

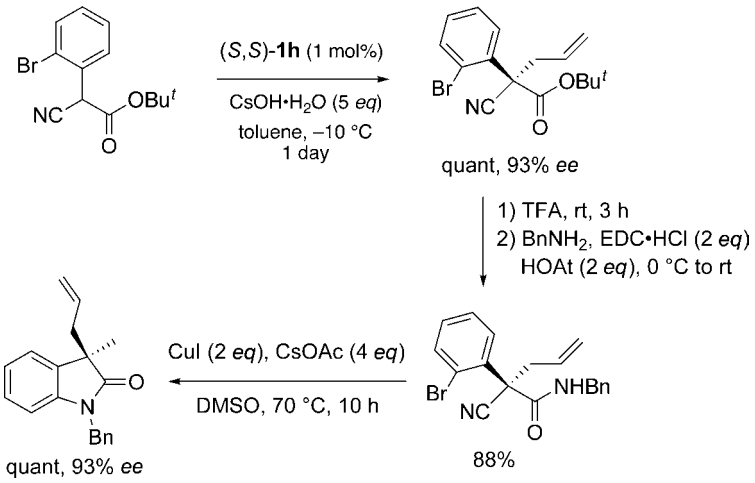
This approach has been successfully applied to the facile synthesis of 3,3-disubstituted oxyindoles as useful building blocks for the synthesis of oxyindole alkaloid, as illustrated in Scheme 5.33.

A highly enantioselective alkylation of 3,5-diaryloxazolidin-2,4-diones **70** with *N*-spiro chiral quaternary ammonium bromide (*S*,*S*)-**69** was achieved under mild phase-transfer conditions. With this methodology in hand, a wide range of tertiary α-hydroxy-α-aryl carboxylic acid derivatives may easily be obtained in good yields and high enantiomeric excesses (Scheme 5.34) [35].

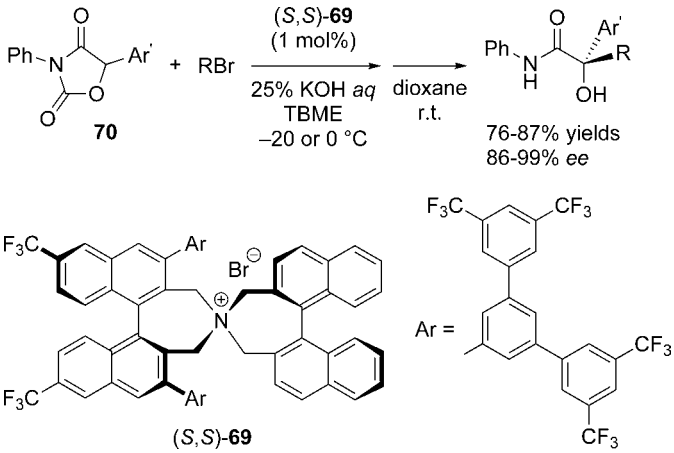
Table 5.9 Asymmetric phase-transfer alkylation of cyanocarboxylates.



Entry	68 (R^1)	R–X	Catalyst	Yield (%)	*ee* (%) (config.)
1	Me	$PhCH_2Br$	(*R*,*R*)-**1e**	98	93
2			(*R*,*R*)-**1h**	96	97 (*R*)
3		$CH_2{=}CHCH_2I$	(*R*,*R*)-**1e**	99	89 (*R*)
4			(*R*,*R*)-**1h**	90	92 (*R*)
5		ICH_2CO_2Et	(*R*,*R*)-**1h**	97	85
6	$CH_2{=}CHCH_2$	MeI	(*R*,*R*)-**1e**	81	67 (*S*)
7		$PhCH_2Br$	(*R*,*R*)-**1h**	99	>99
8		ICH_2CO_2Et	(*R*,*R*)-**1h**	99	90



Scheme 5.33

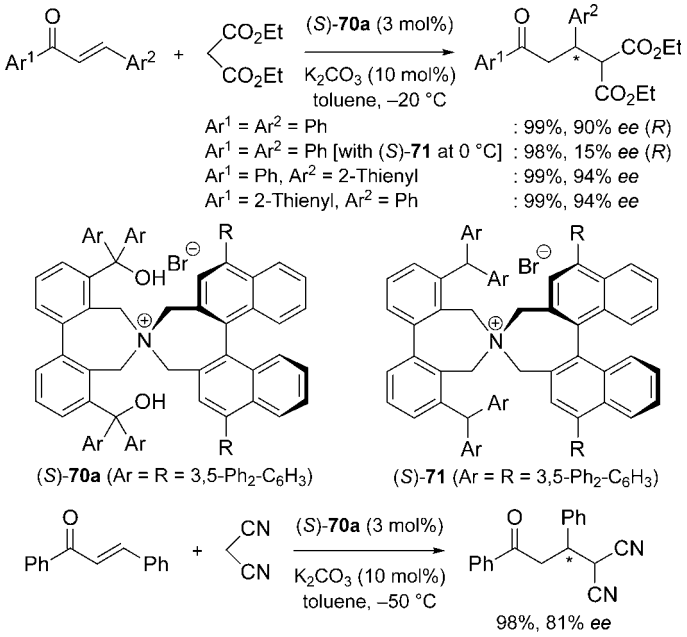


Scheme 5.34

5.3 Michael Addition

The asymmetric Michael addition of active methylene or methine compounds to electron-deficient olefins, particularly α,β-unsaturated carbonyl compounds, represents a fundamental – yet useful – approach to construct functionalized carbon frameworks [36].

Recently, Maruoka and coworkers addressed the importance of dual-functioning chiral phase-transfer catalysts such as **70a** for obtaining a high level of enantioselectivity in the Michael addition of malonates to chalcone derivatives (Scheme 5.35) [37]. For instance, the reaction of diethyl malonate with chalcone in

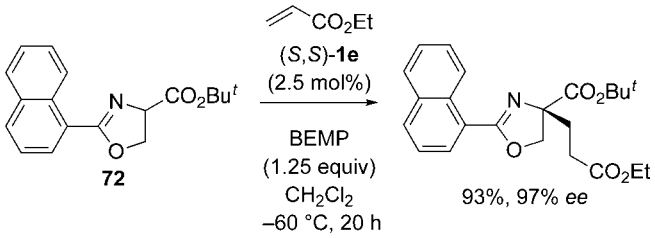


Scheme 5.35

toluene under the influence of K_2CO_3 and (*S*)-**70a** (3 mol%) proceeded smoothly at −20 °C with excellent enantioselectivity, whereas the selectivity was markedly decreased when (*S*)-**71** possessing no hydroxy functionality was used as catalyst. This system is applicable to the Michael addition of malononitrile, as included in Scheme 5.35.

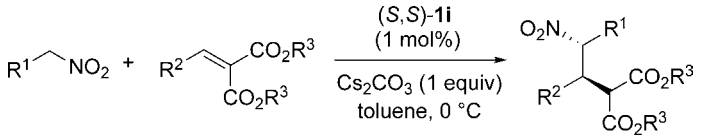
Jew and Park achieved a highly enantioselective synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid, a potent metabotropic receptor ligand, through the Michael addition of 2-naphthalen-1-yl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **72** to ethyl acrylate under phase-transfer conditions [38]. As shown in Scheme 5.36, the use of BEMP as a base at −60 °C with the catalysis of *N*-spiro chiral quaternary ammonium bromide **1e** appeared to be essential for attaining an excellent selectivity.

Maruoka and coworkers developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates under mild phase-transfer conditions



Scheme 5.36

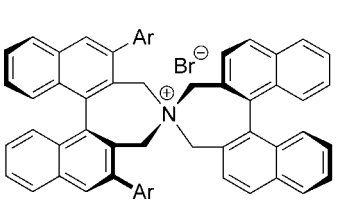
Table 5.10 Asymmetric conjugate addition of nitroalkanes to alkylidenemalonates under phase-transfer conditions.



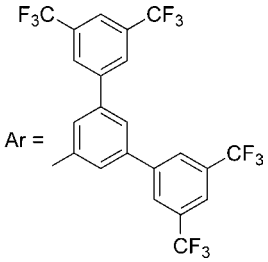
Entry	Nitroalkane (R^1)	Malonate (R^2, R^3)	Reaction time (h)	Yield (%)	*anti/syn* ratio	*ee* (%)
1	Et	Ph, Et	2	99	81:19	94
2	Et	Ph, *i*-Pr	2.5	99	86:14	97
3	Et	Ph, *t*-Bu	24	21	59:41	82
4[a)]	Et	Ph, *i*-Pr	12	99	86:14	97
5	Et	*p*-F-C_6H_4, *i*-Pr	1	99	89:11	98
6	Et	*p*-MeO-C_6H_4, *i*-Pr	3	97	89:11	96
7	Et	2-Naph, *i*-Pr	3	99	86:14	96
8	Et	*c*-Hex, *i*-Pr	10	99	85:15	95
9	Me	Ph, *i*-Pr	2.5	99	80:20	97
10	*i*-Pr	Ph, *i*-Pr	5	99	95:5	99
11	$BnOCH_2CH_2$	Ph, *i*-Pr	2	99	85:15	96

[a)] With 0.1 mol% of (*S*,*S*)-**1i** and 2 equiv. of Cs_2CO_3.

by the utilization of appropriately designed chiral quaternary ammonium bromide **1i** as an efficient catalyst (Table 5.10) [39].

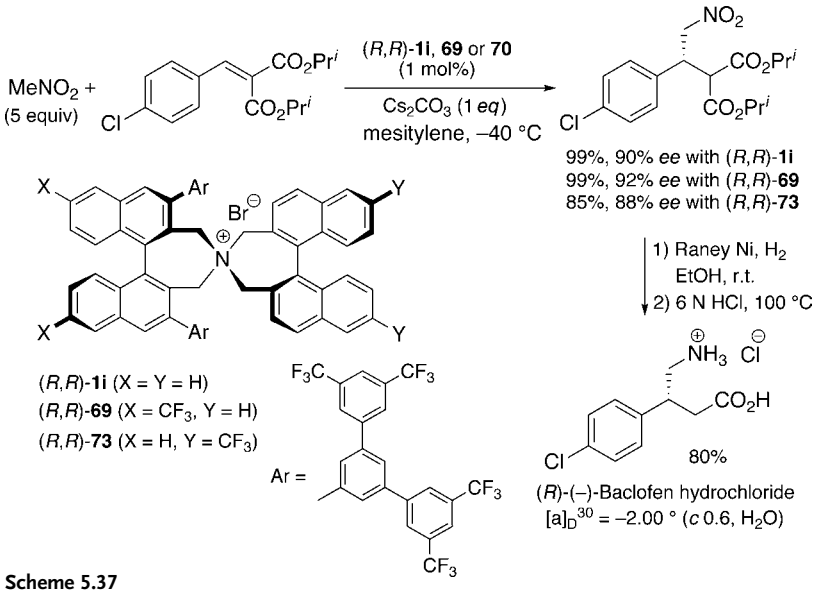


(*S*,*S*)-**1i**

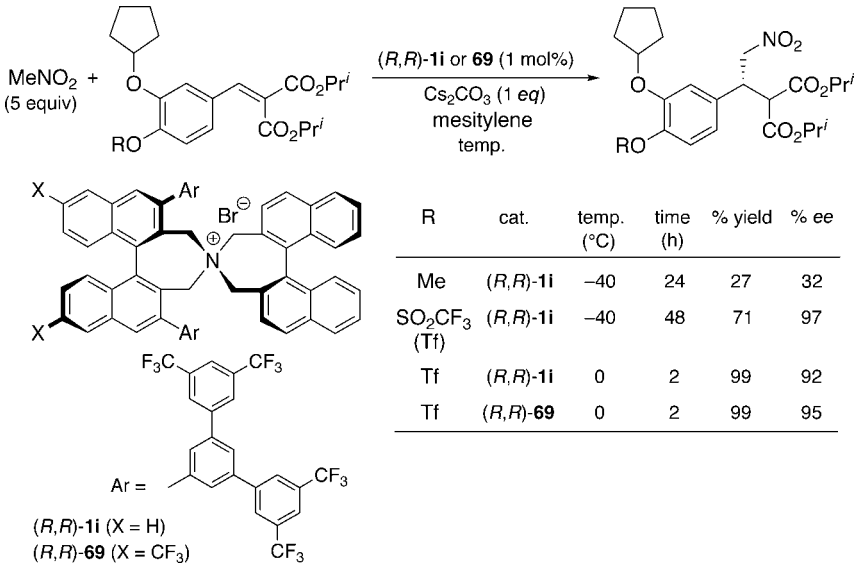


In the case of nitromethane, the observed enantioselectivity is not excellent, and the use of a low reaction temperature and mesitylene as solvent in place of toluene are recommended. In particular, the introduction of an electron-withdrawing trifluoromethyl substituent on the catalyst **1i** further enhanced the enantioselectivity. This new protocol offers a practical entry to optically active γ-amino acid derivatives, as shown in Scheme 5.37 [39a].

A similar tendency is also observed in the asymmetric conjugate addition of nitromethane to α,β-unsaturated malonate (Scheme 5.38), with the chiral conjugate adduct being transformed to (*R*)-Rolipram (Scheme 5.39) [39a].



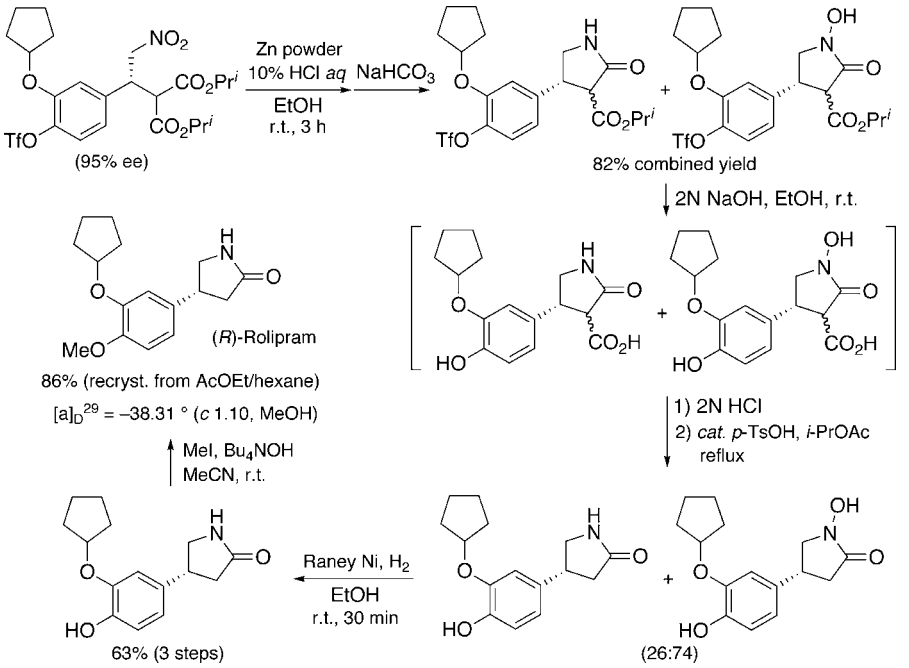
Scheme 5.37



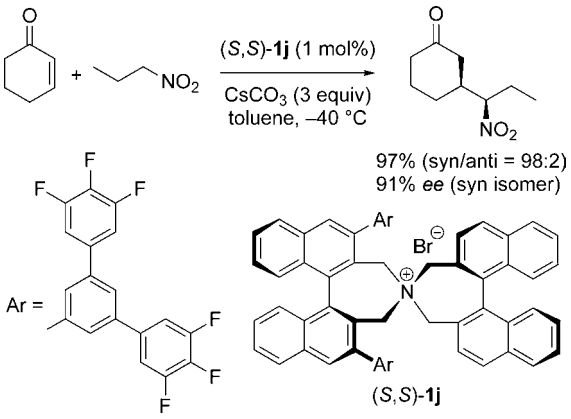
R	cat.	temp. (°C)	time (h)	% yield	% *ee*
Me	(*R*,*R*)-**1i**	–40	24	27	32
SO_2CF_3 (Tf)	(*R*,*R*)-**1i**	–40	48	71	97
Tf	(*R*,*R*)-**1i**	0	2	99	92
Tf	(*R*,*R*)-**69**	0	2	99	95

Scheme 5.38

As an extension of this research, Maruoka and coworkers succeeded in the catalytic asymmetric conjugate addition of nitroalkanes to cyclic α,β-unsaturated ketones under phase-transfer conditions (Scheme 5.40) [39]. Here, the use of 3,5-bis(3,4,5-trifluorophenyl)phenyl-substituted catalyst (*S*,*S*)-**1j** is crucial for obtaining the high enantioselectivity.

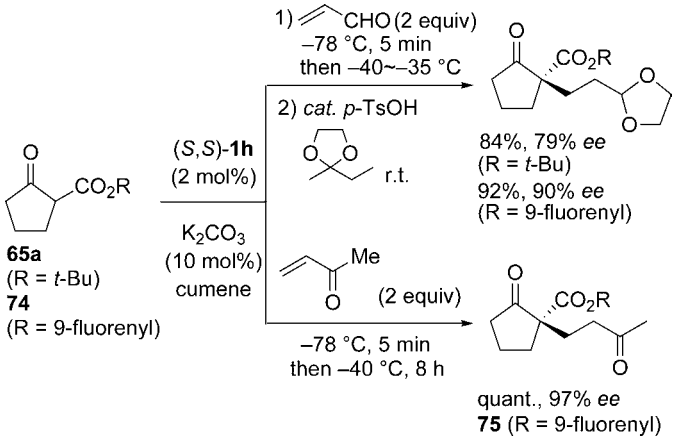


Scheme 5.39



Scheme 5.40

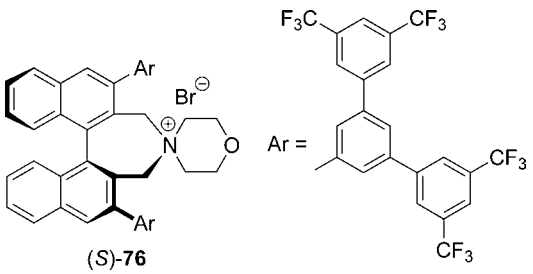
As mentioned above, the enantioselective Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds represents a useful method for the construction of densely functionalized chiral quaternary carbon centers. One characteristic feature of designer chiral phase-transfer catalyst **1h** in this type of transformation is that it enables the use of α,β-unsaturated aldehydes as an acceptor, leading to the



Scheme 5.41

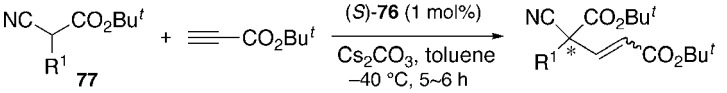
construction of a quaternary stereocenter having three different functionalities of carbonyl origin, as demonstrated in the reaction with 2-*tert*-butoxycarbonylcyclopentanone **65a**. It is of interest that the use of fluorenyl ester **74** greatly improved the enantioselectivity. The addition of **74** to methyl vinyl ketone (MVK) was also feasible under similar conditions, and the desired **75** was obtained quantitatively with 97% *ee* (Scheme 5.41) [32].

Asymmetric conjugate addition of α-substituted-α-cyanoacetates **77** to acetylenic esters under phase-transfer conditions is somewhat of a challenge, because of the difficulty encountered in controlling the stereochemistry of the product. In addition, despite numerous examples of the conjugate additions to alkenoic esters, no successful asymmetric conjugate additions to acetylenic esters have been reported to date. In this context, Maruoka and coworkers recently developed a new morpholine-derived phase-transfer catalyst (*S*)-**76** and applied it to the asymmetric conjugate additions of α-alkyl-α-cyanoacetates **77** to acetylenic esters, as indicated in Table 5.11 [40]. In this asymmetric transformation, an all-carbon quaternary stereocenter can be constructed with a high enantiomeric purity.



(*S*)-**76**

Table 5.11 Enantioselective conjugate addition of cyanoacetates to acetylenic esters under phase-transfer conditions.



Entry	Cyanoacetate (R^1)	Yield (%)	*E*/*Z* ratio	*ee* (%) of *E*/*Z* isomers (config.)
1	$PhCH_2CH_2$	99	3.6:1	94/84
2	$CH_3CH_2CH_2CH_2$	90	3.8:1	95/95
3	$CH_3CH_2CH_2$	21	4.6:1	94/93
4	CH_3CH_2	99	4.6:1	95/–
5	CH_3	99	6.7:1	93 (*S*)/–
6	$(CH_3)_2CH$	97	5.4:1	96/–
7	$CH_2{=}CHCH_2CH_2$	99	3.3:1	92/89
8	$CH_2{=}CHCH_2$	99	6.2:1	92/81
9	$(CH_3)_2CHCH_2CH_2$	99	3.8:1	95/93
10	$(CH_3)_3SiCH_2CH_2$	96	5.1:1	95 (*S*)/93
11	Ph	89	2.2:1	18/–

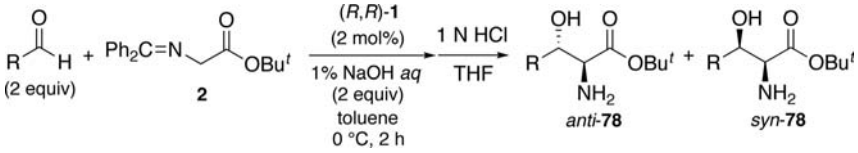
5.4 Aldol Reaction

Although phase-transfer catalytic enantioselective direct aldol reactions of glycine donor with aldehyde acceptors may provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids (which are extremely important chiral units, especially from a pharmaceutical viewpoint), the examples reported to date have been very limited [41].

Maruoka and coworkers recently developed an efficient, highly diastereo- and enantioselective direct aldol reaction of glycine Schiff base **2** with a wide range of aliphatic aldehydes under mild phase-transfer conditions employing *N*-spiro chiral quaternary ammonium salt **1i** as a key catalyst, as shown in Table 5.12 [41a].

Hydrocinnamaldehyde and heptanal were found to be good candidates, indicating the feasibility of direct asymmetric synthesis of lipophilic β-hydroxy-α-amino acids. The reaction with α-triisopropylsiloxyacetaldehyde cleanly produced the desired β-hydroxy-α-amino esters **78** ($R = CH_2OSiPr^i_3$), with virtually complete stereochemical control (*anti*/*syn* = >96 : 4; 98% *ee* for *anti* isomer), which parallels the L-threonine aldolase-catalyzed aldol reaction used for synthesis of the monolactam antibiotic carunoman and its analogues. In contrast, however, an inexplicably limited general applicability of this system was also revealed. The reaction of **2** with 4-benzyloxybutanal gave the aldol product **78** ($R = CH_2CH_2CH_2OBn$), which is a key intermediate for the synthesis of mycestericin D, with low diastereoselectivity (*anti*/*syn* = 58:42; 82% *ee* for *anti* isomer). The use of isovaleraldehyde as an acceptor

Table 5.12 Direct asymmetric aldol reactions of **2** with aldehydes under phase-transfer conditions.



Entry	R	Catalyst	Yield (%)	*anti*/*syn*	*ee* (%) (*anti*)
1	$PhCH_2CH_2$	(*R*,*R*)-**1h**	78	73:27	90
2	$PhCH_2CH_2$	(*R*,*R*)-**1i**	71	92:8	96
3	$CH_3(CH_2)_4CH_2$	(*R*,*R*)-**1i**	65	91:9	91
4	$^{i}Pr_3SiOCH_2$	(*R*,*R*)-**1i**	72	>96:4	98
5	$BnOCH_2CH_2CH_2$	(*R*,*R*)-**1i**	73	58:42	82
6	$(CH_3)_2CHCH_2$	(*R*,*R*)-**1i**	81	37:63	15

showed a preference for the *syn* isomer (*anti*/*syn* = 37:63), and a poor enantiomeric excess was observed for the *anti* isomer.

Mechanistic investigations revealed the intervention of a highly stereoselective retro aldol reaction, which could be minimized by using a catalytic amount of 1% NaOH aqueous solution and ammonium chloride, leading in turn to the establishment of a general and practical chemical process for the synthesis of optically active anti-β-hydroxy-α-amino esters **78** (Table 5.13) [41b].

5.5 Mannich Reaction

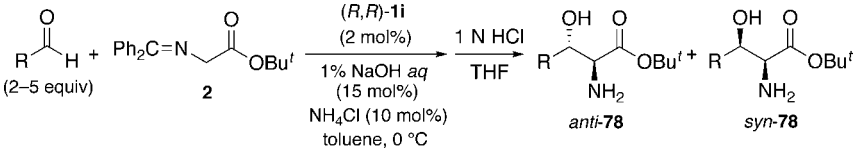
Phase-transfer-catalyzed direct Mannich reaction of glycine Schiff base **2** with α-imino ester **79** was achieved with high enantioselectivity by the utilization of *N*-spiro chiral quaternary ammonium bromide **1e** as catalyst (Table 5.14) [42].

This method enables the catalytic asymmetric synthesis of differentially protected 3-aminoaspartate, a nitrogen analogue of dialkyl tartrate, the utility of which was demonstrated by the product *syn*-**80** being converted into a precursor **81** of streptolidine lactam (Scheme 5.42).

5.6 Neber Rearrangement

The Neber rearrangement of oxime sulfonates has been considered to proceed via a nitrene pathway or an anion pathway. If the latter mechanism is operative, the use of a certain chiral base might result in the discrimination of two enantiotropic α-protons to furnish optically active α-amino ketones. Verification of this hypothesis was provided by realizing the asymmetric Neber rearrangement of simple oxime sulfonate **83**,

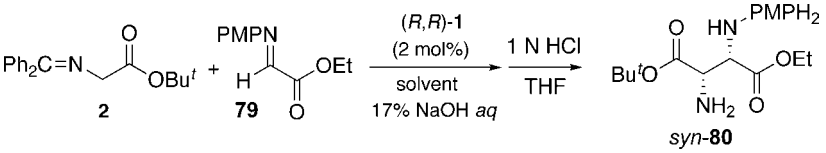
Table 5.13 Direct asymmetric aldol reactions of **2** with a wide range of aldehydes under the improved reaction conditions.



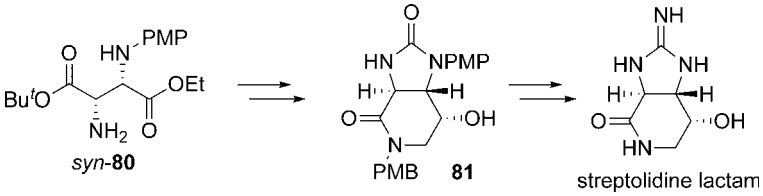
Entry	R	Reaction time (h)	Yield (%)	*anti*/*syn*	*ee* (%) (*anti*)
1	$PhCH_2CH_2$	1.5	82	96:4	98
2	$CH_3(CH_2)_4CH_2$	10	80	94:6	97
3	$CH_3(CH_2)_3CH_2$	10	79	>96:4	97
4	$^iPr_3SiOCH_2$	4.5	73	>96:4	98
5	$BnOCH_2CH_2CH_2$	2	83	96:4	96
6	$(CH_3)_2CHCH_2$	10	64	>96:4	96
7	$CH_2{=}CHCH_2CH_2$	3	82	96:4	98
8	CH_3	8	54	>96:4	99
9	$(CH_3)_2CH$	10	39	>96:4	98
10	$(CH_3)_2CH$	5	70	96:4	98
11	$c\text{-}C_6H_{11}$	3	83	>96:4	98
12	Ph	10	58	47:53	25

generated *in situ* from the parent oxime (*Z*)-**82**, under phase-transfer conditions using the structurally rigid, *N*-spiro-type chiral quaternary ammonium bromide **1j** or **1k** as catalyst. The corresponding protected α-amino ketone **84** was subsequently isolated in high yield, with a notable enantiomeric excess (Scheme 5.43) [43].

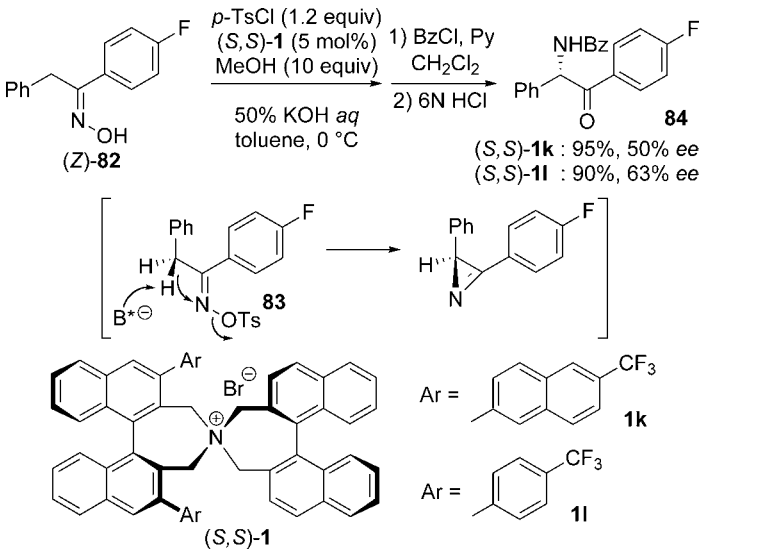
Table 5.14 Direct asymmetric Mannich reaction of **2** with α-imino ester under phase-transfer conditions.



Entry	Catalyst	Solvent	Conditions (°C, h)	Yield (%)	*syn*/*anti*	*ee* (%) (*syn*)
1	(*R*,*R*)-**1h**	Toluene	0, 6	~0		
2	(*R*,*R*)-**1h**		0, 6	41	74:26	79
3	(*R*,*R*)-**1h**		−20, 6	73	79:21	85
4	(*R*,*R*)-**1e**		−20, 6	79	76:24	87
5	(*R*,*R*)-**1j**		−20, 6	49	80:20	50
6	(*R*,*R*)-**1h**	Mesitylene	−20, 6	88	82:18	84
7	(*R*,*R*)-**1e**		−20, 6	88	82:18	91



Scheme 5.42

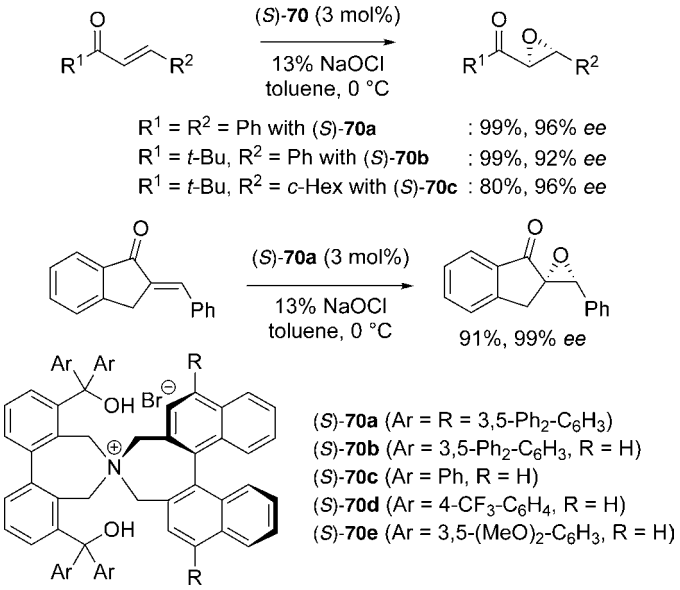


Scheme 5.43

5.7 Epoxidation

The catalytic asymmetric epoxidation of electron-deficient olefins, particularly α,β-unsaturated ketones, has been the subject of numerous investigations, and as a result a number of useful methodologies have been elaborated [44]. Among these, the method utilizing chiral phase-transfer catalysis occupies a unique position in terms of its practical advantages. Moreover, it also allows the highly enantioselective epoxidation of trans-α,β-unsaturated ketones, particularly chalcone.

Maruoka and coworkers designed a new and highly efficient chiral *N*-spiro-type quaternary ammonium salt (*S*)-**70** with dual functions for the asymmetric epoxidation of various enone substrates (Scheme 5.44) [45]. The exceedingly high asymmetric induction is ascribable to the molecular recognition ability of the catalyst toward enone substrates by virtue of the appropriately aligned hydroxy functionality, as well as the chiral molecular cavity. Indeed, the observed enantioselectivity depends heavily



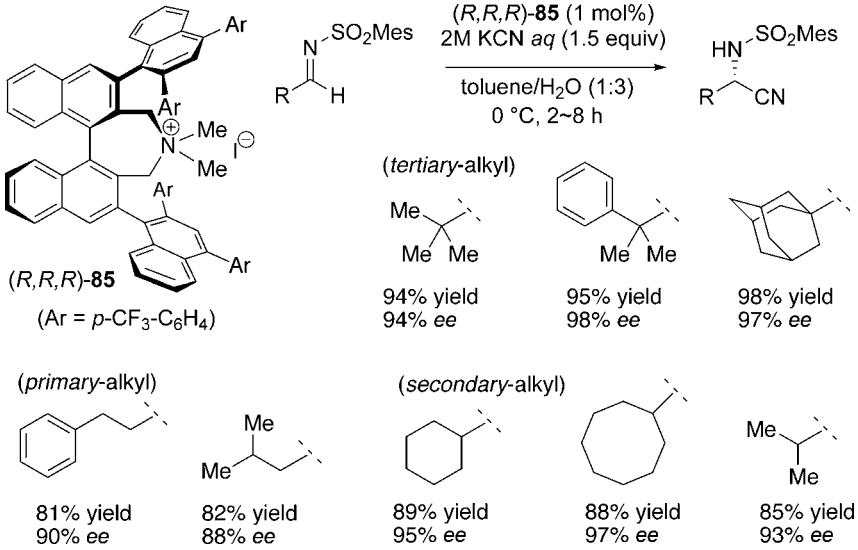
Scheme 5.44

on the steric size and the electronic factor of both Ar and R substituents in (*S*)-**70**, and the use of (*S*)-**70c**∼**e** significantly decreased the enantioselection (61∼66% *ee* for chalcone epoxidation).

5.8 Strecker Reaction

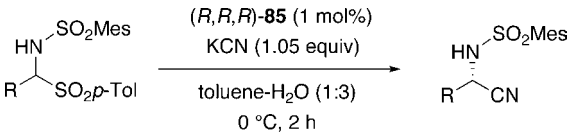
The catalytic asymmetric cyanation of imines – the Strecker reaction – represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. Numerous recent efforts in this field have resulted in the establishment of highly efficient and general protocols, although the use of either alkylmetal cyanide or anhydrous hydrogen cyanide, generally at low temperature, is inevitable. In this regard, Maruoka and coworkers reported the first example of a phase-transfer-catalyzed, highly enantioselective Strecker reaction of aldimines using aqueous KCN, based on the molecular design of chiral quaternary ammonium salts **85** bearing the tetranaphthyl backbone as a remarkably efficient catalyst (Scheme 5.45) [46].

This phase-transfer-catalyzed asymmetric Strecker reaction is further elaborated by the use of α-amido sulfone as a precursor of *N*-arylsulfonyl imine. In this system, the reaction can be conducted with a slight excess of potassium cyanide (1.05 equiv.), and the reaction leads to completion within 2 h (Table 5.15) [46b].



Scheme 5.45

Table 5.15 Direct asymmetric Strecker reaction of α-amido sulfones under phase-transfer conditions.



Entry	α-Amido sulfone (R)	Yield (%)[a)]	*ee* (%)[a)]
1	*c*-Hexyl	99 (89)	97 (95)
2	*c*-Octyl	99 (88)	98 (97)
3	*i*-Pr	99 (85)	97 (93)
4	$PhCH_2CH_2$	99 (81)	94 (90)
5	$(CH_3)_2CHCH_2$	99 (82)	91 (88)

[a)] Values in parentheses refer to the use of sulfonylimines in place of α-amido sulfones.

5.9 Conclusions

The development of various types of chiral phase-transfer catalyst relies largely on the molecular design of both natural product-derived and purely synthetic chiral quaternary ammonium salts. This approach often delivers not only higher reactivity

and stereoselectivity, but also new synthetic opportunities, thus expanding the applicability of asymmetric phase-transfer catalysis in modern organic synthesis. Continuous efforts are made towards an understanding of the relationship between the structure of the catalyst and its activity and stereocontrolling ability. The systematic accumulation of such knowledge would allow even more rational catalyst design in order to pursue selective chemical synthesis both reliably and in a practical manner. In this way it should, in future, be possible to establish genuinely sustainable chemical processes within the context of any forthcoming paradigm shift in the worldwide production of valuable chemical materials.

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6
Two-Center Chiral Phase-Transfer Catalysts for Asymmetric Synthesis

Masakatsu Shibasaki and Takashi Ohshima

6.1
Introduction

As described in the preceding chapters, asymmetric phase-transfer catalysis is one of the most important and useful methods in synthetic organic chemistry, due mainly to its preparative advantages, such as simple reaction procedures, mild conditions, use of inexpensive and environmentally friendly reagents, and ease in scaling-up of the reaction. Pioneering studies by the Merck group [1] and the group of O'Donnell [2] led to the development of a highly practical enantioselective alkylation using Cinchona alkaloid ammonium salts. In the early studies of asymmetric phase-transfer catalysis, therefore, cinchona alkaloid derivatives were primarily examined as chiral catalysts that afforded impressive enantioselectivity for a range of reactions (see Chapters 2 and 3). In 1999, Maruoka *et al.* reported a highly efficient asymmetric phase-transfer catalysis using chiral spiro ammonium salts derived from 1,1′-bi-2-naphthol (BINOL) [3] (see Chapter 5). Subsequently, various efficiently designed chiral phase-transfer catalysts were developed (see Chapter 7). In this chapter, the efforts made towards the development of a novel two-center chiral phase transfer catalyst [4], based on a multifunctional catalyst concept [5], are described, together with details of other important contributions [6–10] in this field.

6.2
Design and Synthesis of Two-Center Chiral Phase-Transfer Catalyst

Previously, a wide variety of metal-mediated asymmetric two-center catalyses based on a multifunctional catalyst concept was developed [5]. Similar to an enzyme reaction, the synergistic functions of two or more active sites in multimetallic catalysts make substrates more reactive, and control their position in the transition state so that the functional groups are proximal to each other. In order to extend this concept to asymmetric organocatalysis, two ammonium salt moieties were

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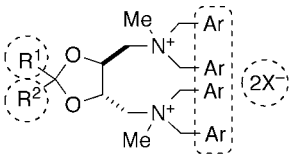
introduced to the catalyst, with an appropriate distance being maintained between them (two-center organocatalyst), where the substrate could be fixed in a chiral environment by two cationic moieties. Shortly before the first report of a two-center chiral phase-transfer catalyst in 2002 [4a], Jew and Park *et al.* [6] and Nájera *et al.* [7] reported dimeric and trimeric cinchona alkaloid-derived chiral phase-transfer catalysts (see Chapter 4). The high enantioselectivities of those catalysts, however, contributed to the steric hindrance of the counter cinchona unit in a similar manner as the *N*-anthracenylmethyl-substituted ammonium salts reported by Lygo *et al.* [11] and Corey *et al.* [12] (see Chapter 4). In addition, when one cinchona unit is located adjacent to another such unit (e.g., in an *ortho*-dimer), poor enantioselectivity is obtained [6]. Thus, those dimeric and trimeric catalysts do not meet the requirements for the ideal two-center catalyst.

In order to achieve an ideal complexation of the two-center catalyst and substrate (glycine Schiff base), a 1,4-diammonium salt rather than a 1,2-diammonium salt or a 1,3-diammonium salt was selected, based on the spatial environment created by the two cationic moieties and several preliminary investigations. Thus, a new two-center catalyst was designed – tartrate-derived diammonium salt (TaDiAS **1**) (Figure 6.1) – both enantiomers of which can be synthesized from commercially available and relatively inexpensive L- or D-tartrate [4a]. Preliminary molecular mechanics (MM) simulations using the Monte Carlo method on Cerius^2 (Accelrys Inc.) [13] supported this hypothesis (Figure 6.2) [4a]. Although a naked enolate is thought preferentially to form *E*-enolate [12], it was expected that the two-center catalyst TaDiAS **1** might form a tight complex with the *Z*-enolate of the glycine Schiff base through several hydrogen bonds. Based on molecular orbital calculations performed by Reetz *et al.*, the positive charge of the tetraalkylammonium cation (R_4N^+) was expected to be delocalized on the α-carbon and hydrogen atoms [14]; that is, not on the nitrogen atom. Moreover, the presence of hydrogen bonds between the α-methylene units of the tetrabutylammonium cations and enolate oxygen atoms, making the anions and cations interact in a highly ordered manner, was revealed by several X-ray structural analyses [14a]. The magnitude of the stabilizing interaction of an aliphatic C−H bond attached to an ammonium nitrogen and a carbonyl oxygen (R_3N^+−C−H···O=C) was evaluated by Houk *et al.* using *ab-initio* calculations [15]. Further, *ab-initio*



(*S*,*S*)-TaDiAS **1a**: $R^1 = R^2$ = Me, Ar = Ph, $X^- = I^-$
(*S*,*S*)-TaDiAS **1b**: R^1 = *t*-Bu, R^2 = Me, Ar = C_6H_4-4-OMe, $X^- = I^-$
(*S*,*S*)-TaDiAS **1c**: R^1 = *t*-Bu, R^2 = Me, Ar = C_6H_4-4-OMe, $X^- = BF_4^-$
(*S*,*S*)-TaDiAS **1d**: $R^1 = R^2$ = Pr, Ar = C_6H_4-4-Me, $X^- = I^-$
(*S*,*S*)-TaDiAS **1e**: $R^1 = R^2$ = Pr, Ar = C_6H_4-4-Me, $X^- = BF_4^-$
(*S*,*S*)-TaDiAS **1f**: $R^1 = R^2 = CH_2CH_2C_6H_4$-4-F, Ar = C_6H_4-4-Me, $X^- = BF_4^-$

Figure 6.1 The structure of TaDiAS **1**.

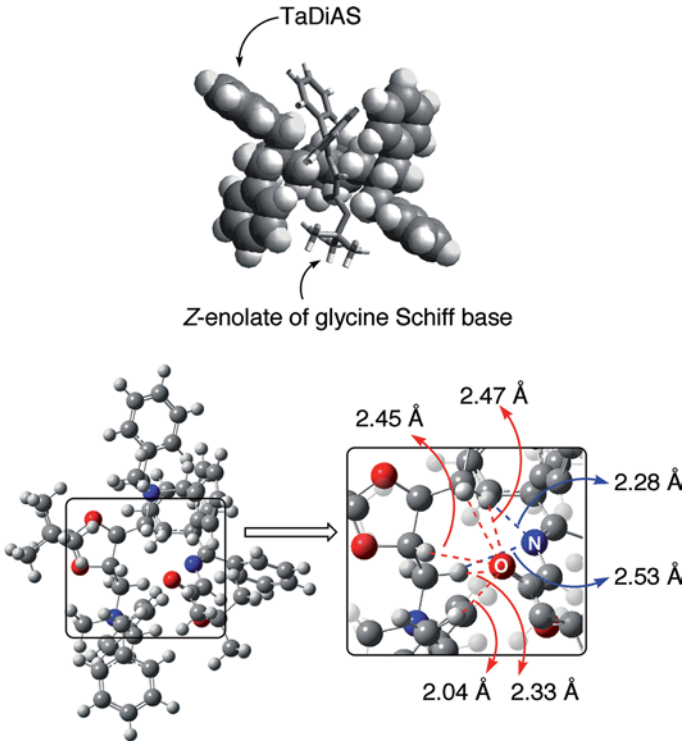


Figure 6.2 Results of molecular mechanics (MM) simulation (top) and density functional theory (DFT) calculation (bottom).

calculations at the HF/3-21G level [4a] and density functional theory (DFT) calculations at the B3LYP/6-31G** level [16] also supported these assumptions.

Similar to the success achieved with TADDOLs (see Chapter 8) [17], many chiral catalysts and chiral ligands were synthesized from tartaric acid, which provides a proper C_2-symmetric framework and structural diversity. TaDiAS **1** has remarkable structural diversity because a wide variety of catalysts can be easily synthesized by changing the acetal moieties (R^1 and R^2), aromatic parts (Ar), and counter anions (X^-), making it possible to fine-tune, three-dimensionally, the catalyst (*vide infra*). Other candidates, such as **2**, **3**, and **4** (Figure 6.3), produced unsatisfactory results (<10% ee) during preliminary catalyst screening of the *N*-substituents [4a]. Thus,

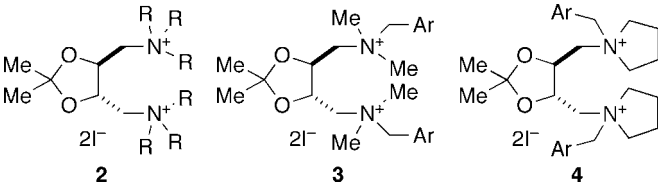
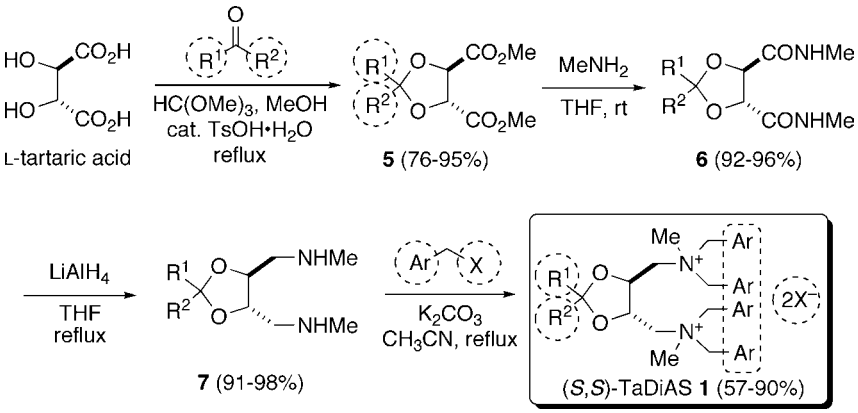


Figure 6.3 Other candidates for the two-center catalyst.



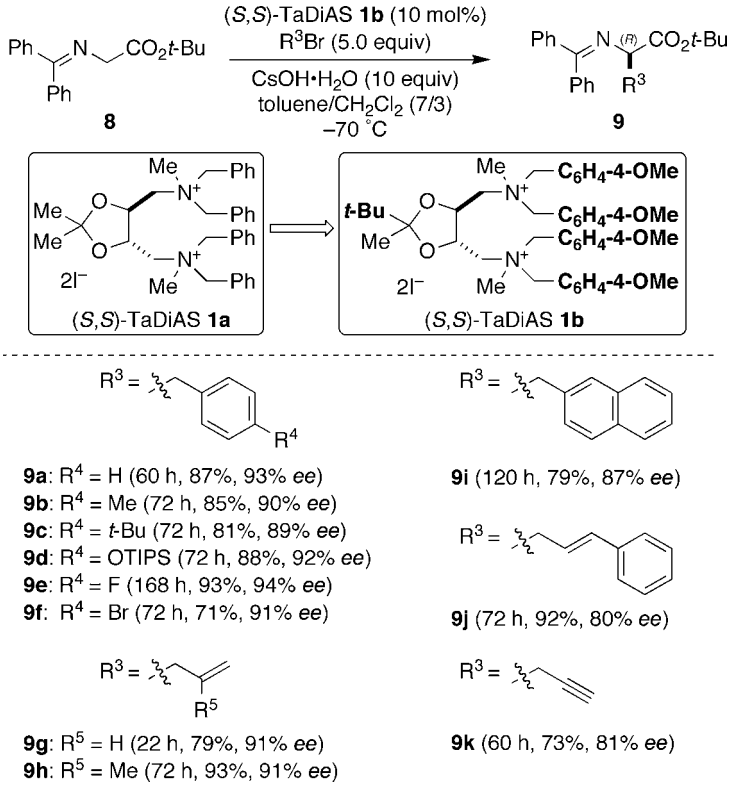
Scheme 6.1 Second-generation synthesis of TaDiAS **1**.

it was hypothesized that the combination of two large *N*-substituents and one small *N*-substituent such as TaDiAS **1** would be best for the phase-transfer catalyst of a glycine Schiff base.

The second-generation synthesis of (*S*,*S*)-TaDiAS **1** is summarized in Scheme 6.1 [16]. This process requires only common and inexpensive reagents under operationally simple reaction conditions. When using the first-generation synthesis (a five-step process from diethyl tartrate) [4a] or the second-generation synthesis (a four-step process from tartaric acid), a variety of catalysts with versatility on the acetal moieties (R^1 and R^2) and aromatic parts (Ar) were synthesized (over 100 derivatives) [18]. A large-scale reaction (>20 g) can also be performed with the same efficiency.

6.3 Catalytic Asymmetric Phase-Transfer Alkylation

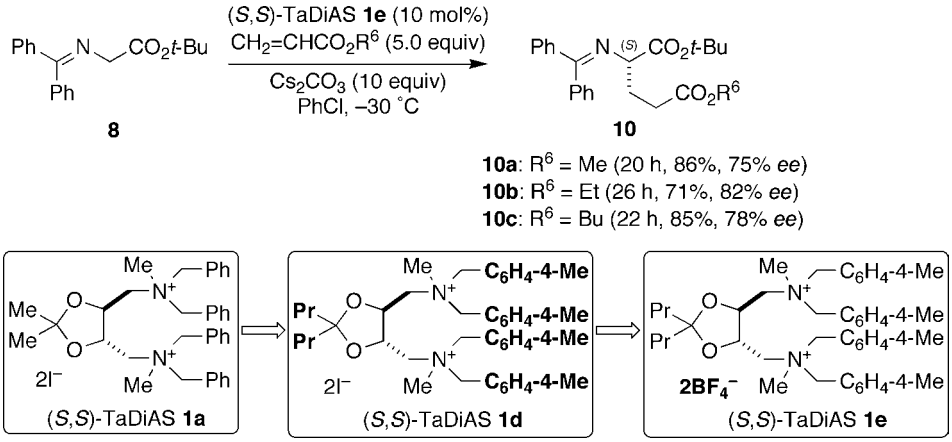
Subsequently, a variety of TaDiAS **1** in the phase-transfer alkylation of glycine Schiff base **8** was examined (Scheme 6.2). Starting from the original TaDiAS **1a**, the effect of an acetal moiety was examined. Contrary to expectation, a better phase-transfer alkylation was obtained when un-C_2-symmetric catalysts ($R^1 \neq R^2$) were used. Among these, the catalyst with a *tert*-butyl methyl acetal had the highest selectivity. By retaining the acetal moiety as a *tert*-butyl methyl acetal, the effect of the aromatic part was examined. Screening of the aromatic part revealed that TaDiAS **1b** (Ar = 4-methoxyphenyl) gave the best result. After optimization of the reaction conditions, the scope and limitations of the different electrophiles were examined. For example, when 10 mol% of TaDiAS **1b** was used with cesium hydroxide, all phase-transfer alkylations of **8** with benzyl, allyl, and propargyl reagents proceeded at −70 °C in good to high enantiomeric excess (ee) [4]. In all cases, when (*S*,*S*)-TaDiAS **1b** was used as the catalyst, the absolute configurations of the products were *R*.



Scheme 6.2 Catalytic asymmetric phase-transfer alkylation of various electrophiles.

6.4
Catalytic Asymmetric Phase-Transfer Michael Addition to α,β-Unsaturated Esters

The next phase was to investigate the catalytic asymmetric phase-transfer Michael reaction of **8** to acrylate. The results of catalyst screening for the phase-transfer Michael reaction revealed that, in contrast to the above-mentioned phase-transfer alkylation, a C_2-symmetric catalyst gave better results than an un-C_2-symmetric catalyst. In this reaction, 4-methylphenyl was the best aromatic substituent and TaDiAS **1d** ($R^1 = R^2 = Pr$) gave the highest ee-values (75–82% ee) (Scheme 6.3) [4a]. Using (*S,S*)-TaDiAS **1d**, the obtained Michael product **10** had an *S* configuration in all cases (opposite to that of alkylation products). Although the phase-transfer Michael reaction, in principle, requires only a catalytic amount of base, most reported phase-transfer Michael reactions are performed in the presence of excess base. In the case of the catalyst system for the Michael reaction, a decrease in Cs_2CO_3 from 10 to 0.5 equiv. resulted in lower selectivity, although reactivity was maintained. At this stage, it was expected that the counter anion of TaDiAS **1** would affect the reactivity in the catalytic base system. A variety of new types of TaDiAS **1** with hard counter anions



Scheme 6.3 Catalytic asymmetric phase-transfer Michael addition and counter anion effects.

instead of iodide were prepared, and hard counter anions were seen dramatically to accelerate the phase-transfer Michael reaction. Among the examined counter anions, tetrafluoroborate catalyst **1e** had the highest reactivity with improved enantioselectivity [4b]. Moreover, using only 1 mol% of the catalyst **1e** (X=BF_4) gave much higher reactivity than 10 mol% of **1d** (X=I) at 4 °C. To the best of the present authors' knowledge, this is the first example of such dramatic counter anion effects in phase-transfer catalysis. Moreover, in phase-transfer alkylation with excess hydroxide, there was a moderate counter anion effect [4b]. The tetrafluoroborate catalyst **1c** had a higher reactivity than the iodide catalyst **1b**, though this may be a characteristic property of the two-center phase-transfer catalyst. Even when the catalyst forms a complex with enolate, one counter anion should remain just beside the catalyst. These results clearly demonstrated that fine-tuning of the catalyst **1** could be realized by changing not only the acetal moieties (R^1 and R^2) and aromatic parts (Ar), but also the counter anions (X^-) (i.e., three-dimensional fine-tuning).

6.5
Catalytic Asymmetric Phase-Transfer Michael Addition to Enones

In contrast to the Michael reaction to α,β-unsaturated esters, the addition of a glycine Schiff base to α,β-unsaturated ketones (enones) proceeds with more modest selectivity (up to 60% ee), due to the uncatalyzed background reaction [4f]. In order to improve enantioselectivity, conformational investigations were performed of (*S*,*S*)-TaDiAS **1e** to gain further insight into the factors influencing enantioselectivity [4e]. An X-ray crystallographic analysis of **1e** revealed that each tetrafluoroborate is located very close to each of the ammonium units, creating an attractive C_2-symmetrical chiral environment (Figure 6.4). Another interesting fact is that alkyl chains of the acetal moiety snake up in a direction perpendicular to the dioxolane ring. A previous examination of the substituent effects on asymmetric phase-transfer catalyses

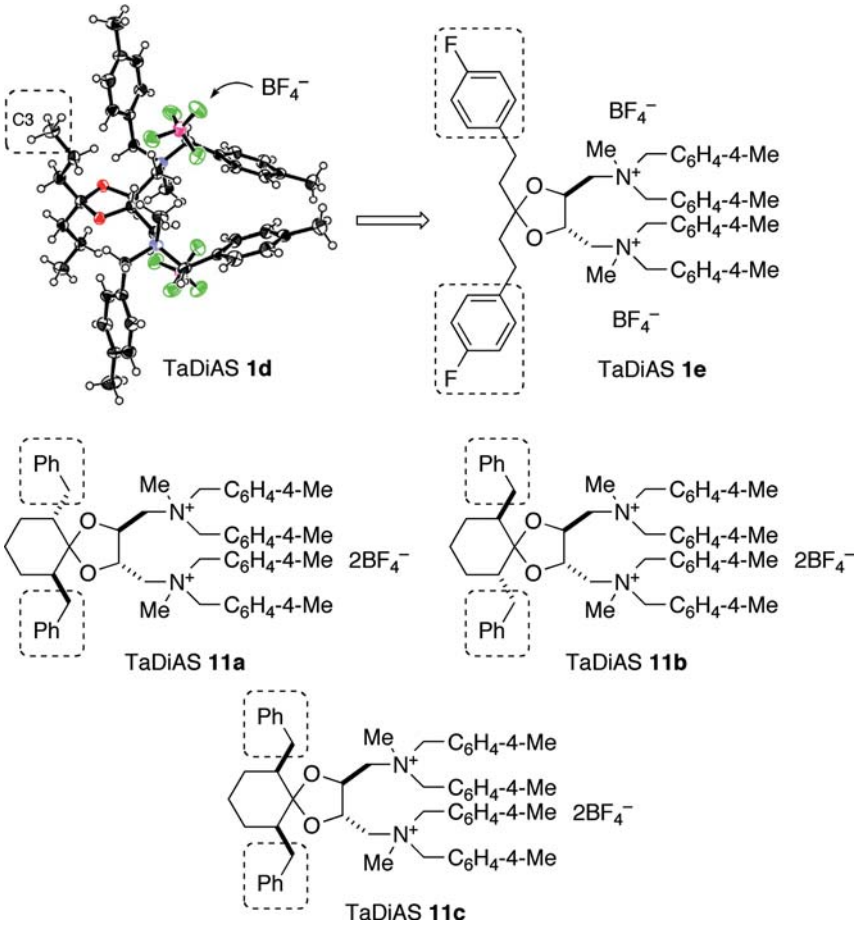
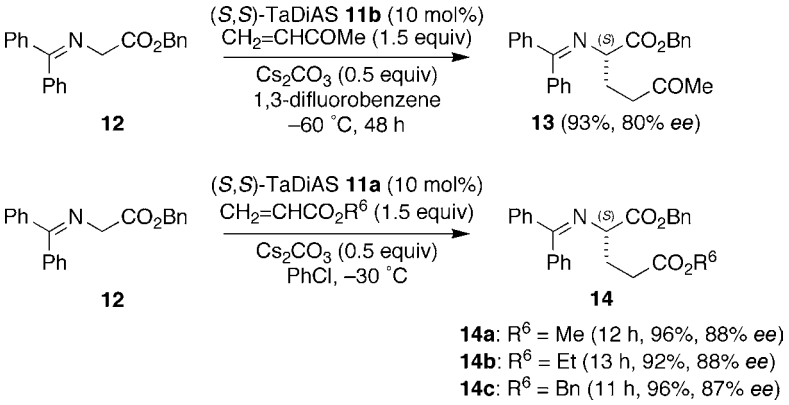


Figure 6.4 The crystal structure of TaDiAS **1d** and the structures of **1e**, **11a–c**.

revealed that both the aromatic and acetal moieties strongly affected enantioselectivity [4a]. This unexpected strong substituent effect of the acetal moiety may be understood by the close proximity between the counter anions and acetal side chains, especially the C2- and C3-positions. Thus, it was assumed that sterically congested acetal substituents would prevent an unfavorable approach of electrophiles to the enolate of the glycine Schiff base. On the basis of this hypothesis, (*S*,*S*)-TaDiAS **1f** – which had an aromatic ring at the C3 position of the acetal side chains – was developed for an asymmetric Mannich-type reaction (*vide infra*) [4e]. Even when using **1f**, however, the enantiomeric excess was still moderate in the Mannich-type reaction, and was not further improved in the asymmetric Michael reaction [4f]. Recently, the catalysts **11a–c** were introduced that had a 2,6-disubstituted cyclohexane structure at the acetal moiety, to affect the chiral environment more strongly around quaternary ammonium salts. (*S*,*S*)-TaDiAS **11b** efficiently catalyzed an asymmetric Michael

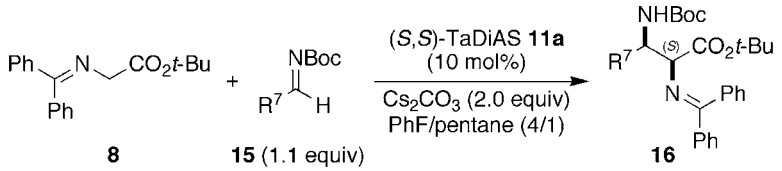


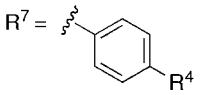
Scheme 6.4 Catalytic asymmetric phase-transfer Michael addition using TaDiAS **11**.

reaction of glycine Schiff base **12** to enone (Scheme 6.4) [4f,g]. Moreover, the enantioselectivities of asymmetric Michael reaction of **12** to α,β-unsaturated esters were also improved, in which TaDiAS **11a** gave better results than TaDiAS **11b** (24 h, 68% yield, 83% *ee* for **14a**) [4g].

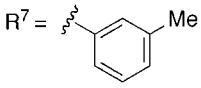
6.6
Catalytic Asymmetric Phase-Transfer Mannich-Type Reaction

α,β-Diamino acids are key structural components in molecules such as peptides, β-lactam antibiotics, and in other medicinally relevant compounds. Various preparation methods of optically active α,β-diamino acid derivatives have been reported, but almost all of these require the use of stoichiometric amounts of chiral sources. More direct and atom-economically favorable methods using a Mannich-type reaction of a glycine Schiff base with imines were reported by Jørgensen *et al.* [19] and Maruoka *et al.* [20]. Recently, using the TaDiAS-promoted phase-transfer catalysis, the successful development of a highly enantio- and diastereoselective Mannich-type reaction of a glycine Schiff base with an *N*-Boc imine was completed, to afford a variety of optically active *syn*-α,β-diamino acid derivatives (Scheme 6.5) [4e]. Selection of the imine protecting group was pivotal for achieving high diastereoselectivity, for example: *N*-diphenylmethyl imine, no reaction; *N*-benzyl imine, no reaction; *N*-diphenylphosphinoyl imine, moderate diastereoselectivity; and *N*-tosyl imine, moderate diastereoselectivity and low enantioselectivity. As mentioned in Section 6.5, the introduction of a 4-fluorophenyl group at the C3 position of the acetal side chains (TaDiAS **1f**) improved enantioselectivity of the Mannich-type reaction as compared with TaDiAS **1e** [4e]. Furthermore, (*S*,*S*)-TaDiAS **11a**, which has a 2,6-disubstituted cyclohexane structure at the acetal moiety, efficiently catalyzed the Mannich-type reactions of various aromatic imines **16a–h** as well as enolizable aliphatic imines **16i** and **16j** in high yield with higher diastereoselectivity and enantioselectivity, compared with TaDiAS **1e** [4e].

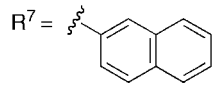




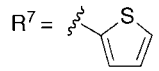
16a: R^4 = OMe (–45 °C, 96%, dr 99/1, 90% *ee*)
16b: R^4 = Me (–45 °C, 92%, dr 99/1, 88% *ee*)
16c: R^4 = H (–45 °C, 66%, dr 99/1, 79% *ee*)
16d: R^4 = F (–30 °C, 94%, dr 97/3, 81% *ee*)
16e: R^4 = Cl (–20 °C, 88%, dr 98/2, 70% *ee*)



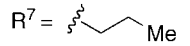
16f (–45 °C, 94%, dr 99/1, 73% *ee*)



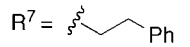
16g (–45 °C, 96%, dr 97/3, 69% *ee*)



16h (–30 °C, 89%, dr 98/2, 83% *ee*)



16i (–30 °C, 95%, dr >20/1, 71% *ee*)



16j (–30 °C, 89%, dr >20/1, 75% *ee*)

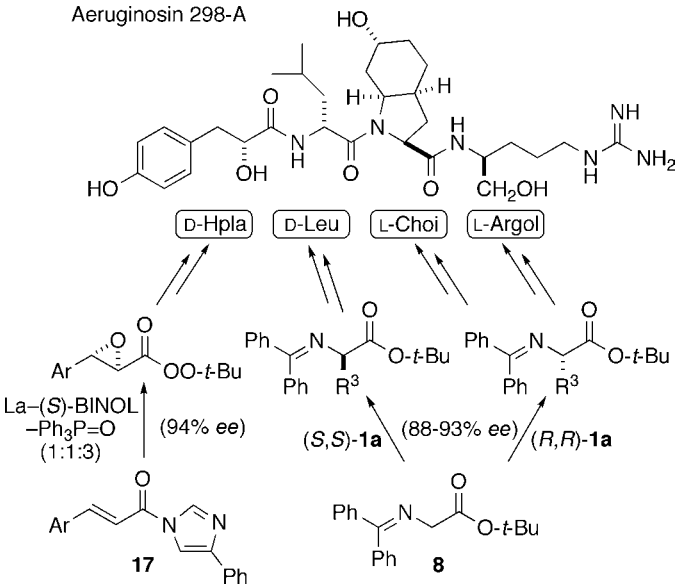
Scheme 6.5 Catalytic asymmetric phase-transfer Mannich-type reaction.

6.7
Synthetic Applications

After having optimized the practical asymmetric phase-transfer catalysis using TaDiAS with broad substrate generality, the synthetic applications of the procedure to create complex natural products was examined, based on the easy accessibility to a variety of optically active natural and unnatural α-amino acids.

6.7.1
Enantioselective Syntheses of Aeruginosin 298-A and its Analogues

Aeruginosin 298-A was selected as a target compound based on its unique serine protease inhibitor activity, and the existence of non-standard amino acids such as 2-carboxy-6-hydroxyoctahydroindole (Choi) within the molecule (Scheme 6.6). In order to gain insight into the structure–activity relationships, a highly versatile synthetic method was developed for aeruginosin 298-A as well as its analogues, using the above-mentioned catalytic asymmetric phase-transfer alkylation for the syntheses of the D-Leu, L-Choi, and L-Algol portions. Likewise, the catalytic asymmetric epoxidation of α,β-unsaturated imidazolide, which was previously developed by the authors' group [21], was used for synthesis of the (*R*)-3-(4-hydroxyphenyl)lactic acid (D-Hpla) portion [4b,c]. Because most of the aeruginosin families contain a D-Hpla portion, an L-Choi portion, and a guanidine unit, a variety of analogues was synthesized by

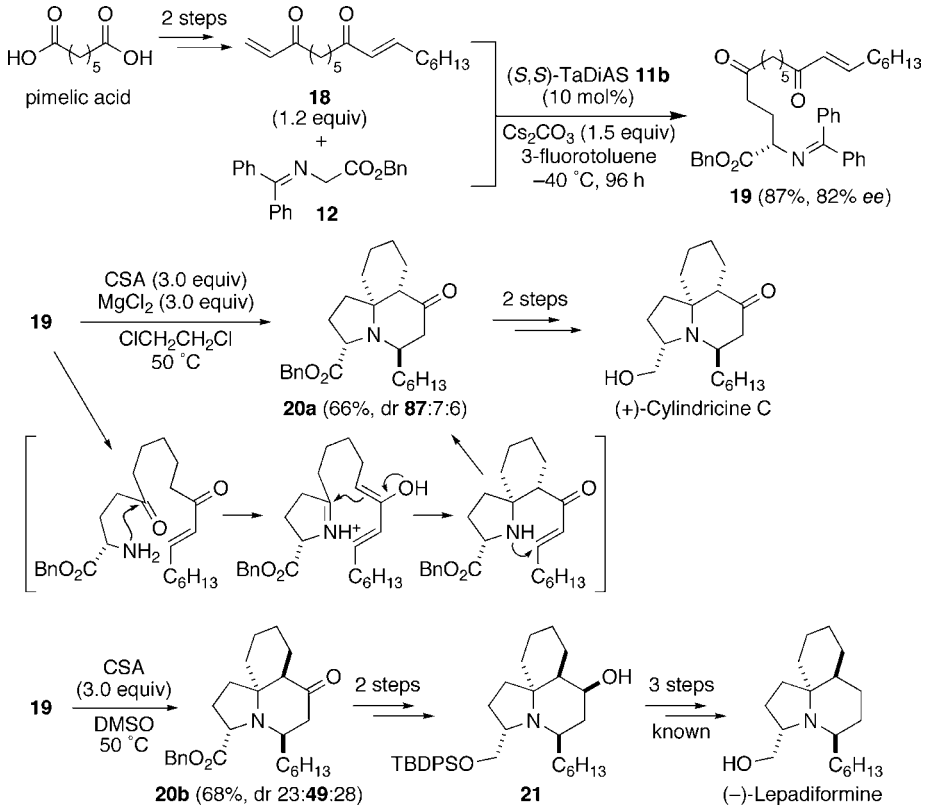


Scheme 6.6 Enantioselective synthesis of aeruginosin 298-A.

altering the D-Leu and L-Algol portions. The biologic activity studies of the newly synthesized aeruginosin analogues against the serine protease trypsin suggested that conformation of the Argol portion, and especially the guanidine side chain, is extremely important for the inhibitory activity [4c].

6.7.2
Short Syntheses of (+)-Cylindricine and Formal Synthesis of (–)-Lepadiformine

Tandem reactions, in which several transformations are combined in a single procedural step, are powerful tools for minimizing the number of synthetic steps [22]. In addition to time–cost benefits, tandem reactions allow for selective reactions of unstable species, whilst side reactions are minimized by the rapid successive formation and consumption of intermediates. In fact, combining the catalytic asymmetric phase-transfer Michael addition of dienone **18** and tandem cyclization, which involves imine formation, Mannich reaction, and aza-Michael reaction, made it possible to synthesize tricyclic alkaloid (+)-cylindricine C in six steps from pimelic acid (Scheme 6.7) [4f,g]. The catalytic asymmetric Michael reaction of glycine Schiff base **12** to dienone **18**, which was prepared from pimelic acid in two steps, was performed with TaDiAS **11b** to give highly functionalized Michael product **19** in 87% yield with 82% ee. The key tandem cyclization was promoted by the treatment of **19** with 10-camphorsulfonic acid (CSA) to give tricyclic compound **20** as a mixture of three diastereomers. The addition of $MgCl_2$ greatly improved the diastereoselectivity to provide the *cis*-fused diastereomer **20a** as the

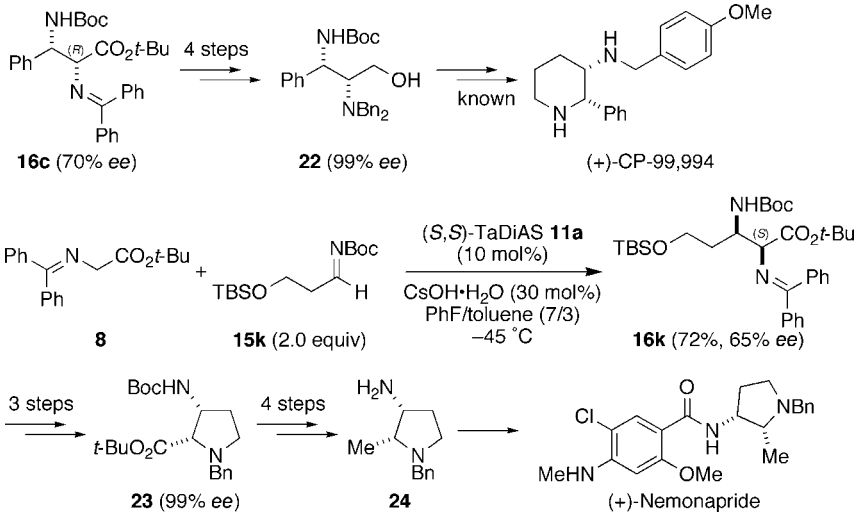


Scheme 6.7 Enantioselective synthesis of (+)-cylindricine and (−)-lepadiformine.

major product, which was then successfully converted to (+)-cylindricine C in two steps (total six steps) [4f,g]. Moreover, tandem cyclization in the absence of magnesium salts preferentially afforded *trans*-fused diastereomer **20b**, leading to a formal synthesis of (−)-lepadiformine [4g].

6.7.3
Formal Synthesis of (+)-CP-99,994 and Total Synthesis of (+)-Nemonapride

Mannich product **16**, prepared by the above-mentioned Mannich-type reaction of glycine Schiff base **8** with *N*-Boc imine **15** (see Section 6.6), is synthetically quite useful because the *N*-diphenylmethylene group and *N*-Boc group of **16** can be readily and chemoselectively deprotected, resulting in easy access to a variety of α,β-diamino acid compounds. For example, Mannich product **16c**, which was synthesized using (*R,R*)-TaDiAS **1e**, was readily converted to key intermediate **22** for synthesis of the selective and potent neurokinin substance P antagonist (+)-CP-99,994 through highly chemoselective deprotection of the *N*-diphenylmethylene group of **16c** [4e].



Scheme 6.8 Total synthesis of (+)-nemonapride.

This chemistry was further applied to the catalytic asymmetric synthesis of the antipsychotic agent (+)-nemonapride [4h]. The synthesis began with a catalytic asymmetric phase-transfer Mannich-type reaction of **8** with alkyl imine **15k**, giving the desired Mannich-product **16k** in 72% yield with 65% ee. This highly functionalized α,β-diamino ester **16k** was then successfully transformed into (+)-nemonapride through a pyrrolidine ring-forming reaction (Scheme 6.8).

6.8 Catalyst Recovery and Reuse

In contrast to commonly used cinchona alkaloid-derived catalysts, TaDiAS is extremely stable under strongly basic conditions. Despite the existence of β-hydrogens to the ammonium cation, catalyst decomposition (such as that due to Hoffman elimination) has not been observed under phase-transfer reaction conditions. This stability might be due to the dihedral angle of approximately 55° between the ammonium cation and β-hydrogen in the stable conformation of TaDiAS (see X-ray structure shown in Figure 6.4). As a result, TaDiAS can be recovered from the reaction mixture in a high yield (80–90%) [4b,d]. After quenching the phase-transfer reaction with water and diethyl ether, the catalyst appeared as a white solid between the two layers. Vigorous stirring for 5 to 10 min resulted in the white solid sticking to the glass walls, such that the solid could easily be separated from the product by simple decantation (Figure 6.5). The residual solid was dissolved with 30% MeOH in CH_2Cl_2 and the solution passed through a paper filter to remove inorganic salts. The catalyst was recovered after solvent evaporation and reused in

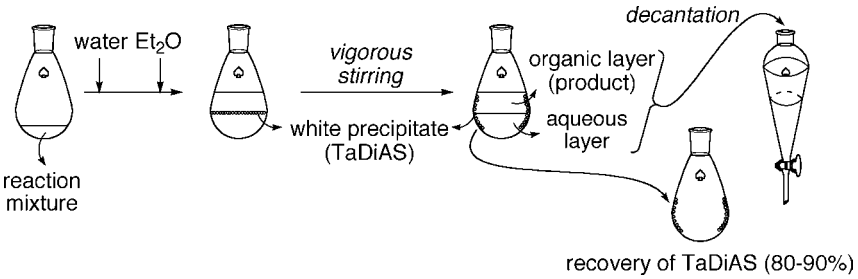
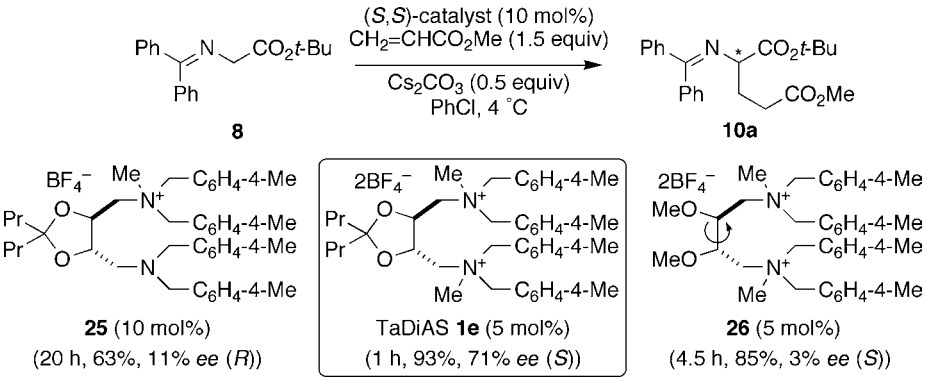


Figure 6.5 A general procedure for the recovery of TaDiAS.

the phase-transfer alkylation, without further purification, demonstrating an unchanged catalyst efficiency.

6.9 Role of Two Ammonium Cations

The precise reaction mechanism remains unclear even after various mechanistic investigations, including kinetic studies and spectroscopic analyses [4]. On the other hand, the role of the two ammonium cations in TaDiAS was clearly demonstrated by the following experiments. The mono-cation catalyst **25** (10 mol%) had a much lower reactivity and selectivity than the di-cation catalyst TaDiAS **1e** (5 mol%) in the phase-transfer Michael addition (Scheme 6.9) [4d]. Moreover, when the relative position of the two ammonium cations was not regulated as in catalyst **26**, the enantioselectivity was quite low [16]. These results suggested that, as expected, the distance between the two ammonium cations is very important, and the enolate of the glycine Schiff base is fixed in a chiral environment by two cationic moieties, verifying that the two-center catalyst concept is reasonable.



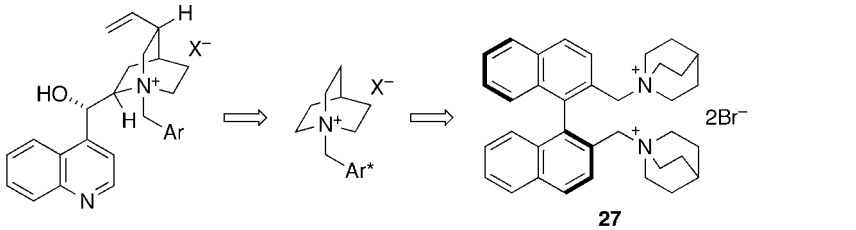
Scheme 6.9 Catalytic asymmetric phase-transfer Michael addition using various ammonium salts.

6.10
Other Two-Center Chiral Phase-Transfer Catalysts

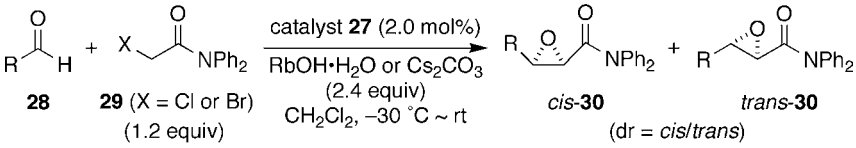
Recently, other types of two-center chiral phase-transfer catalysts were designed, synthesized, and applied to a variety of asymmetric phase-transfer catalyses [8–10].

6.10.1
Two-Center Chiral Phase-Transfer Catalyst Derived from BINOL (1)

In 2004, Arai *et al.* reported a new type of two-center phase-transfer catalyst **27** derived from BINOL (Scheme 6.10) [8]. Previously, a catalytic asymmetric Darzens reaction of α-chloro ketones and a sulfone using a cinchona alkaloid-type phase-transfer catalyst was developed by Shioiri, Arai, and coworkers [23]. Unfortunately, the reaction of α-halocarboxylic acid derivatives such as **29** required more strongly basic conditions, under which cinchona alkaloid-derived ammonium salts gradually decompose. Based on the concept of simplification and modification of the cinchona alkaloid-type catalyst, a binaphthyl skeleton was directly introduced to the quinuclidine nitrogen; a large twist angle between the two naphthyl moieties was expected due to both steric and dipole repulsion between bulky bis-ammonium units in catalyst **27**. The phase-transfer catalyst **27** was readily synthesized from (*S*)-BINOL in four steps, and 2 mol% of the catalyst **27** promoted an asymmetric Darzens reaction of α-haloamides **29** with various aldehydes **28**, in good yields. Although the obtained diastereo- and enantioselectivities were not highly satisfactory, this was the first



27



28 **29** (X = Cl or Br) (1.2 equiv) — (dr = *cis*/*trans*)

30a: R = Ph (81%, dr 2.3, 58% *ee* (*cis*), 63% *ee* (*trans*))
30b: R = C_6H_4-3-Br (81%, dr 2.4, 51% *ee* (*cis*), 60% *ee* (*trans*))
30c: R = C_6H_4-4-OMe (82%, dr 8.1, 62% *ee* (*cis*), 60% *ee* (*trans*))
30d: R = C_6H_4-2-OMe (quant., dr 2.2, 57% *ee* (*cis*), 67% *ee* (*trans*))
30e: R = C_6H_4-2-Me (77%, dr 2.0, 64% *ee* (*cis*), 70% *ee* (*trans*))
30f: R = C_6H_4-4-*t*-Bu (70%, dr 2.8, 63% *ee* (*cis*), 64% *ee* (*trans*))
30g: R = *i*-Pr (77%, dr 4.4, 57% *ee* (*cis*), 40% *ee* (*trans*))
30h: R = *c*-Hex (61%, dr 5.0, 60% *ee* (*cis*), 48% *ee* (*trans*))

Scheme 6.10 Catalytic asymmetric Darzens reaction of α-haloamides.

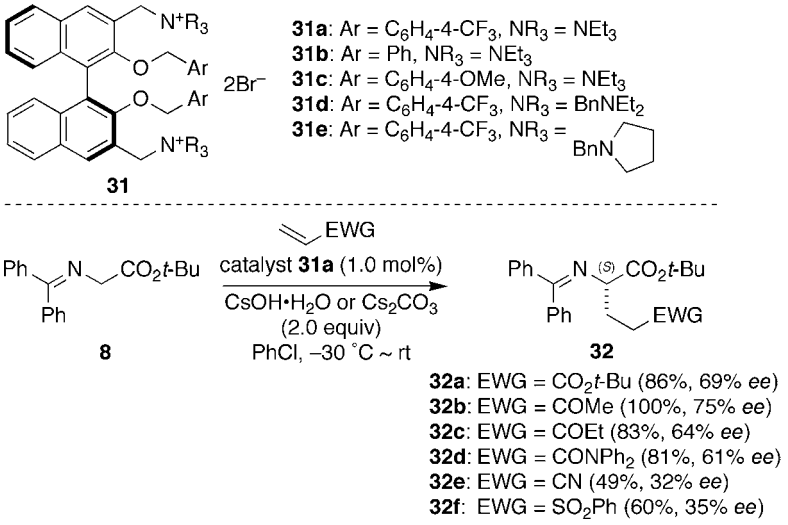
example of a catalytic asymmetric Darzens reaction giving glycidic acid derivatives, thereby indicating the high potential of this type of two-center catalyst in asymmetric reactions.

6.10.2
Two-Center Chiral Phase-Transfer Catalyst Derived from BINOL (2)

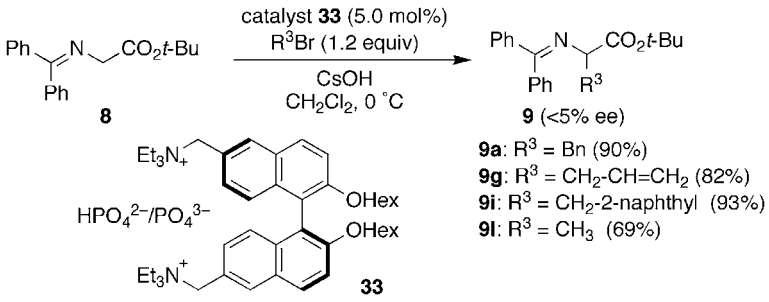
Arai *et al.* also reported another BINOL-derived two-center phase-transfer catalyst **31** for an asymmetric Michael reaction (Scheme 6.11) [8b]. Based on the fact that BINOL and its derivatives are versatile chiral catalysts, and that bis-ammonium salts are expected to accelerate the reaction due to the two reaction sites – thus preventing an undesired reaction pathway – catalyst **31** was designed and synthesized from the di-MOM ether of (*S*)-BINOL in six steps. After optimization of the reaction conditions, the use of 1 mol% of catalyst **31a** promoted the asymmetric Michael reaction of glycine Schiff base **8** to various Michael acceptors, with up to 75% ee. When catalyst **31b** or **31c** was used as a catalyst, a lower chemical yield and selectivity were obtained, indicating the importance of the interaction between π-electrons of the aromatic rings in the catalyst and substrate. In addition, the amine moiety in catalyst **31** had an important role in enantioselectivity (**34d** and **34e**: lower yield and selectivity), while catalyst **31a** gave the best results.

6.10.3
Two-Center Chiral Phase-Transfer Catalyst Derived from BINOL (3)

In the same year, MacFarland reported another BINOL-derived two-center phase-transfer catalyst **33**, in which bis-ammonium units were introduced at the 6,6′



Scheme 6.11 Catalytic asymmetric Michael addition using BINOL-derived two-center catalyst.



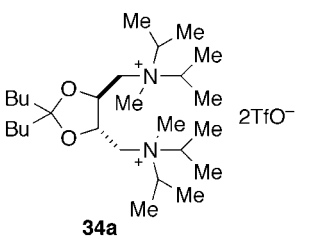
Scheme 6.12 Catalytic asymmetric alkylation using BINOL-derived two-center catalyst.

positions of the BINOL skeleton to act cooperatively (Scheme 6.12) [9]. The catalyst **33** was synthesized from (*R*)-BINOL in five steps and applied to the phase-transfer alkylation of glycine Schiff base **8**. The catalyst activity of **8** was comparable to that of the *N*-spiro binaphthyl phase-transfer catalyst [3], although the enantioselectivities were below 5% for all substrates and conditions.

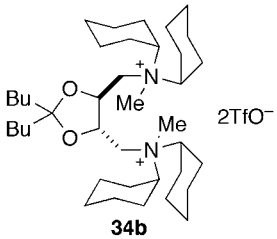
6.10.4
Two-Center Chiral Phase-Transfer Catalyst Derived from Tartrate (1)

MacFarland's group was interested in dicationic catalysts, hypothesizing that the nucleophilic anion interacts with both ammonium centers to provide optimum enantioselectivity, and chose tartaric acid as the source of chirality. Thus, these authors developed tartrate-derived two-center catalysts **34** (the structure of which is related to TaDiAS), but attached a more sterically demanding alkyl group to the nitrogens (Scheme 6.13) [9b]. The catalysts **34** were synthesized from diethyl tartrate in seven steps via the acid chloride. Both two-center catalysts **34a** and **34b** catalyzed the asymmetric phase-transfer alkylation and Michael addition of **8** in good yield, but low enantioselectivity. Interestingly, when catalysts **34** were used as the catalyst, the absolute configurations of both alkylation products and Michael products were *R* (see Section 6.4).

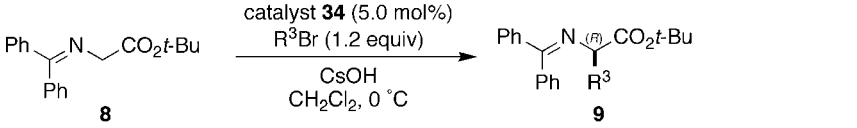
These low selectivities were improved by changing the amine substituents of the catalysts **34** from diisopropyl/dicyclohexyl to C_2-symmetric 2,5-dimethylpyrroline ring, leading to two diastereomeric catalysts **35** (Scheme 6.14), which were synthesized in the same way as catalysts **34** [9]. The catalytic competency of **35** was established using standard phase-transfer alkylation conditions to afford the alkylation product with up to 37% ee. Enantioselectivities obtained using diastereomers of the catalyst **35** were different, but not opposite, which suggests that the stereocenters function cooperatively in one diastereomer, but not in the other.



34a

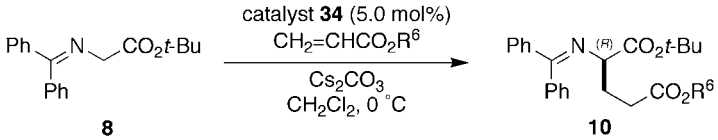


34b



8 **9**

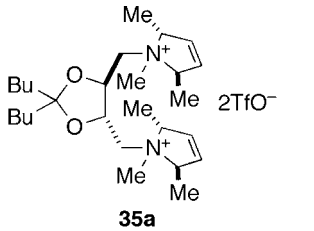
9a: R^3 = Bn (83%, 9% *ee* using **34a**)
9m: R^3 = CH_2-C_6H_4-2-Me (94%, 9% *ee* using **34a**)
9n: R^3 = CH_2-C_6H_4-4-Me (99%, 8% *ee* using **34b**)



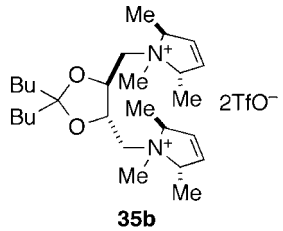
8 **10**

10a: R^6 = Me (100%, 11% *ee* using **34b**)
10b: R^6 = Et (100%, 6% *ee* using **34a**)

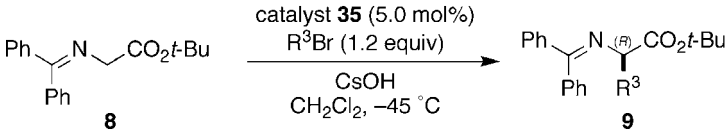
Scheme 6.13 Catalytic asymmetric alkylation and Michael addition using tartrate-derived two-center catalyst.



35a



35b



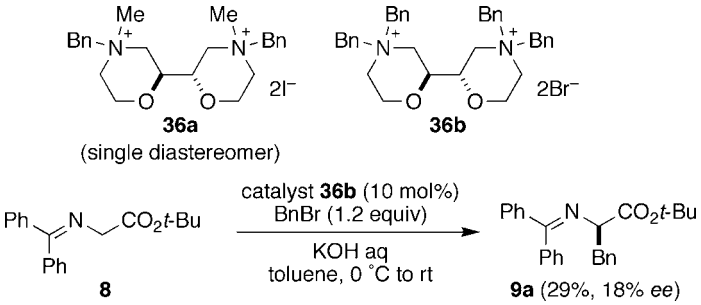
8 **9**

	using **35a**	using **35b**
9a: R^3 = Bn	(73%, 30% *ee* (*R*))	(47%, 26% *ee* (*R*))
9g: R^3 = CH_2-CH=CH_2	(75%, 28% *ee* (*R*))	(72%, 28% *ee* (*S*))
9i: R^3 = CH_2-2-naphtyl	(39%, 12% *ee* (*S*))	(45%, 37% *ee* (*S*))
9l: R^3 = CH_3	(73%, 8% *ee* (*R*))	(50%, 8% *ee* (*S*))
9m: R^3 = CH_2-C_6H_4-2-Me	(85%, 26% *ee* (*R*))	(77%, 9% *ee* (*R*))
9n: R^3 = CH_2-C_6H_4-4-Me	(84%, 19% *ee* (*R*))	(80%, 27% *ee* (*S*))

Scheme 6.14 Catalytic asymmetric alkylation using tartrate-derived two-center catalyst.

6.10.5
Two-Center Chiral Phase-Transfer Catalyst Derived from Tartrate (2)

Very recently, Kanger *et al*. designed and synthesized 2,2′-bimorpholinium ammonium salts **36** as a chiral phase-transfer catalyst [10], based on their previous studies of an organocatalytic Michael addition and an intramolecular aldol condensation reaction [24] (Scheme 6.15). Starting from dimethyl 2,3-*O*-isopropylidene-L-tartrate, the tartaric acid backbone was converted to a C_2-symmetric heterocyclic diammonium salt **36** in six steps, where nitrogen atoms were fixed into a more rigid cyclic, two-centered diammonium structure. Although phase-transfer alkylation of **8** using the catalyst **36a** gave a racemic product, the introduction of more bulky groups at the ammonium site improved enantioselectivity (up to 18% ee), indicating the possibility of further improving selectivity by modifying the *N*-substituents.



Scheme 6.15 Catalytic asymmetric alkylation using 2,2′-bimorpholinium ammonium salts.

6.11
Conclusions

Since the early 2000s, several efficient two-center chiral phase-transfer catalysts have been developed based on different concepts, such as the synergistic function of two ammonium units and the introduction of steric hindrance to prevent nucleophilic attack from an undesired direction. The two-center chiral phase-transfer catalysts reported to date have been prepared from cinchona alkaloid, tartrate, and BINOL. Successful results obtained using these two-center catalysts verified that the above-mentioned two-center catalyst concept is reasonable, and that two-center chiral phase-transfer catalysts are useful in asymmetric synthesis. In order to extend these two-center catalyst concepts to other useful asymmetric catalyses, the rational design of two-center catalysts through further intensive catalyst tuning, together with studies of the structure–catalyst efficiency relationship, computational investigations and mechanistic studies, are essential considerations for the future.

Acknowledgements

The authors thank the Japan Society for the Promotion of Science (JSPS), the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Uehara Memorial Foundation for financial support in the development of TaDiAS described in this chapter. They also thank their co-workers, whose names are acknowledged on the publications from their laboratory and cited therein.

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7
Other Chiral Phase-Transfer Catalysts for Asymmetric Synthesis

Hiroaki Sasai and Mahesh L. Patil

7.1
Introduction

Currently, the chiral phase-transfer catalyst category remains dominated by cinchona alkaloid-derived quaternary ammonium salts that provide impressive enantioselectivity for a range of asymmetric reactions (see Chapter 1 to 4). In addition, Maruoka's binaphthyl-derived spiro ammonium salt provides the best results for a variety of asymmetric reactions (see Chapters 5 and 6). Recently, some other quaternary ammonium salts, including Shibasaki's two-center catalyst, have demonstrated promising results in asymmetric syntheses (see Chapter 6), while chiral crown ethers and other organocatalysts, including TADDOL or NOBIN, have also found important places within the chiral phase-transfer catalyst list (see Chapter 8).

Apart from these well-known catalysts, much effort has been expended in the synthesis and applications of chiral phase-transfer catalysts that include various quaternary ammonium salts, metal–salen complexes, phosphonium salts, and chiral amines. However, few of these catalysts have shown promising levels of asymmetric induction in asymmetric reactions.

The aim of this chapter is to provide up-to-date information on the design and applications of other chiral phase-transfer catalysts.

The history of chiral phase-transfer catalysts begin during the 1970s [1], when the first investigators examined a wide variety of reactions with numerous catalyst structures, based mainly on ephedrine with a β-hydroxyammonium salt-type skeleton. During these early stages, the enantiomeric excess (ee) ranged from only few percent to 50% [2–5], and the situation was further complicated when some of the results were disputed, the suggestion having been made that the reported ee-values were due to optically active catalyst decomposition [6]. The early studies reported independently by the groups of MacIntosh [7] and Dehmlow [8] provided excellent information on the chiral catalyst design, and provided the foundation for further studies on the use of quaternary ammonium salts as chiral phase-transfer catalysts.

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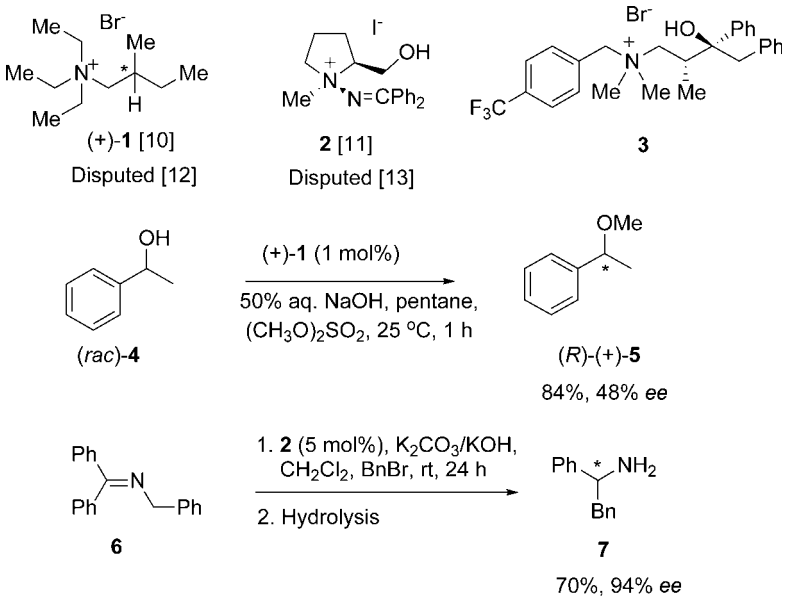
7.2
Other Chiral Phase-Transfer-Catalyzed Reactions

7.2.1
Alkylation

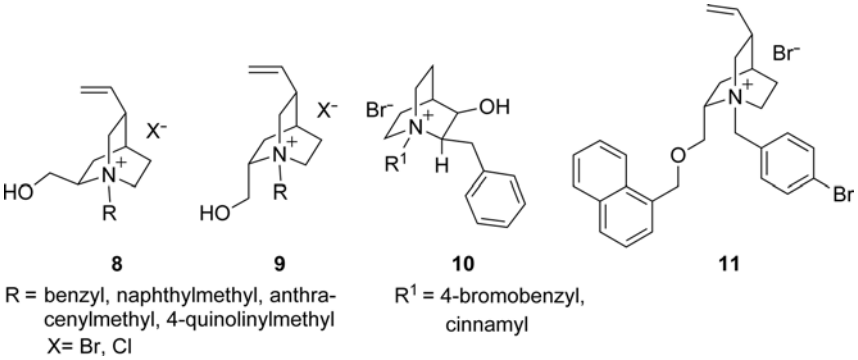
In recent years, much research has been conducted on chiral phase-transfer-catalyzed asymmetric alkylation, following the initial report by the Merck group on the cinchona alkaloid-derived chiral phase-transfer-catalyzed asymmetric alkylation of 2-substituted indanone enolate anion [9]. Based on molecular modeling and X-ray crystal structures, the stereochemistry was rationalized in terms of a tight ion-pair which resulted from the multipoint interaction of the catalyst with the indanone ring that included hydrogen bonding, π–π stacking and van der Waals interactions. These effects contributed to an arrangement where the quinuclidine ring lying behind the plane controlled the approach of electrophiles from the front face (i.e., the bottom-face approach is shielded).

Non-cinchona alkaloid-derived quaternary ammonium salts **1** [10] and **2** [11] were each shown to promote asymmetric alkylation reactions, with enantioselectivity of up to 48% and 94% *ee*, respectively (Scheme 7.1).

These results were disputed, however, when Dehmlow questioned the reproducibility obtained when using catalysts **1** [12] and **2** [13]. In fact, Dehmlow reported the use of quaternary ammonium salt **3** for the asymmetric hydroxylation reaction, with promising levels of enantioselectivity [8d].



Scheme 7.1



Scheme 7.2

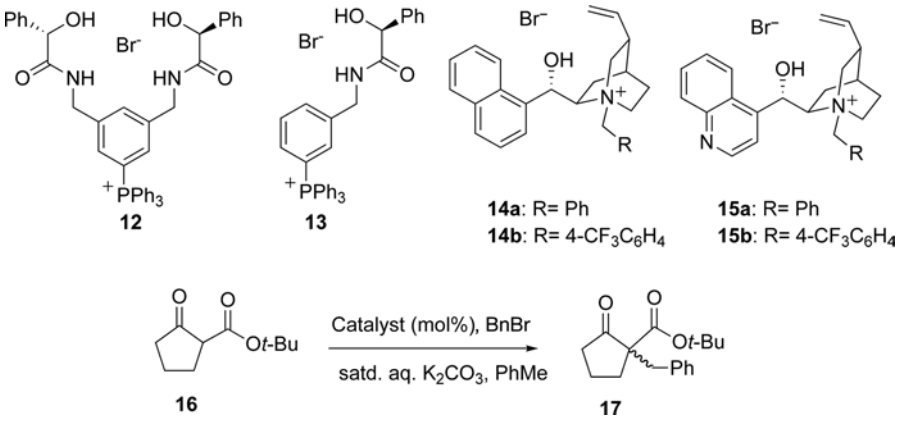
Consequently, Dehmlow and coworkers modified the cinchona alkaloid structure to elucidate the role of each of the structural motifs of cinchona alkaloid-derived chiral phase-transfer catalysts in asymmetric reactions. Thus, the quinoline nucleus of cinchona alkaloid was replaced with various simple or sterically bulky substituents, and the resulting catalysts were screened in asymmetric reactions (Scheme 7.2). The initial results using catalysts **8–11** in the asymmetric borohydride reduction of pivalophenone, the hydroxylation of 2-ethyl-1-tetralone and the alkylation of Schiff's base each exhibited lower enantiomeric excesses than the corresponding cinchona alkaloid-derived chiral phase-transfer catalysts [14].

Later, Manabe introduced the novel concept of using phosphonium salts as chiral phase-transfer catalysts that provide multiple hydrogen bonding sites for the efficient substrate–catalyst ion pairing [15]. The phosphonium salt **12** was designed based on Manabe and colleague's previous studies on the development of artificial receptor molecules [16]. The phosphonium salt **12** consists of two mandelamide units with two –NH and two –OH groups, which are believed to interact with the counter anion through hydrogen bonding, which in turn helps to keep the anion in close proximity to the asymmetric environment. Manabe *et al.* have conducted NMR experiments to support the existence of hydrogen bonding. Finally, the catalytic efficiency of phosphonium salt **12** was investigated in the asymmetric alkylation of *tert*-butyl 2-oxocyclopentanecarboxylate **(16)** under phase-transfer catalysis conditions (Table 7.1).

The asymmetric benzylation of **16** was promoted by phosphonium salt **12** in moderate yield with encouraging levels of enantioselectivity when the catalyst loading was as low as 0.20 mol % (Table 7.1, entry 3). Further, a low temperature improved the enantiomeric excess to 50% *ee* (entry 5). A low enantiomeric excess obtained using the phosphonium salt **13** (entry 6) suggested a critical role for two mandelamide units in the catalytic efficiency of phosphonium salt **12**. Unfortunately, this reaction proved to be highly substrate-sensitive, and other alkylating agents or different ester substituents in **16** afforded low enantioselectivities.

In continuation with their studies on the synthesis of new analogues of cinchona alkaloids, Dehmlow *et al.* prepared quaternary ammonium salt **14**, which is a

Table 7.1 Asymmetric *C*-benzylation of *tert*-butyl 2-oxocyclopentane carboxylate using PTCs **12–15**.



Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)	*ee* (%)	Ref.
1	**12** (5)	20	24	47	38 (*R*)	[15]
2	**12** (1)	20	24	43	39 (*R*)	[15]
3	**12** (0.20)	20	24	37	40 (*R*)	[15]
4	**12** (1)	20	168	80	38 (*R*)	[15]
5	**12** (1)	0	168	44	50 (*R*)	[15]
6	**13** (1)	20	24	63	1 (*S*)	[15]
7	**14a** (5)	r.t.	26	21	52 (*S*)	[17]
8	**14b** (5)	r.t.	26	56	37 (*S*)	[17]
9	**15a** (5)	r.t.	26	97	46 (*S*)	[17]
10	**15b** (5)	r.t.	26	96	31 (*S*)	[17]

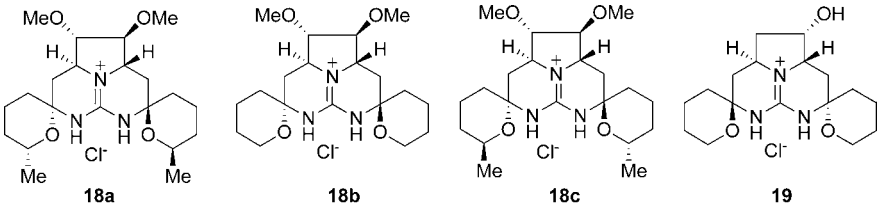
r.t., room temperature.

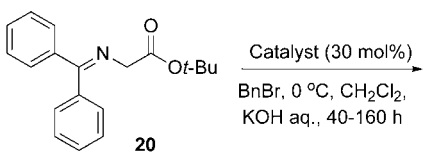
monodeaza analogue of cinchonine-derived catalyst **15**. The quinoline ring of cinchona alkaloid was replaced with a sterically demanding naphthalene ring while keeping other cinchona alkaloid structure intact. The catalysts **14a**,**b** were then tested in the asymmetric alkylation of **16** under phase-transfer catalysis conditions, and their efficiency compared with cinchona alkaloid derivatives **15a**,**b** [17]. Although the reactivity of cinchona alkaloid-derived phase-transfer catalyst **15a** was higher than the monodeaza analogue **14a**, later showed a slightly better enantioselectivity, and product **17** was obtained in 52% *ee* (Table 7.1, entry 7 versus 9). In contrast to other reactions, both the catalysts **14b** and **15b** with *p*-(trifluoromethyl)benzyl susbtituents exhibited a lower enantioselectivity (Table 7.1, entries 8 and 10).

The asymmetric alkylation of Schiff's base ester using a chiral phase-transfer catalyst to produce α-amino acids is one of the most widely studied reactions. This reaction is generally used as a test reaction to design new, efficient chiral

phase-transfer catalysts, and several significant achievements have been realized with enantioselectivities up to 99% *ee* [18].

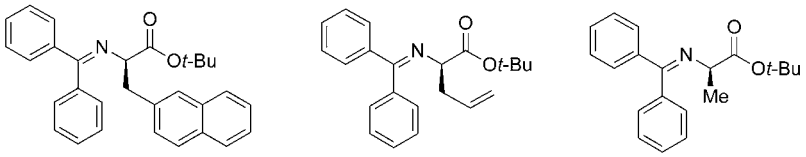
The design and synthesis of a novel C_2-symmetric chiral pentacyclic guanidine-type phase-transfer catalyst based on the natural product ptilomycalin A skeleton has been described by Nagasawa *et al.* [19a]. Various guanidine-type phase-transfer catalysts **18–19** with no substituent (**18b** and **19**) or a methyl substituent (**18a** and **18c**) on the spiro ether rings with different stereochemistries, have been prepared and the structures revealed by X-ray crystallographic analysis. Interestingly, **18a** and **18b** showed a closed-type cavity and indeed, this cavity size – which is controlled by substituents on the spiro ether ring – was found to play a significant role in the asymmetric induction of the enantioselective alkylation reaction. Asymmetric alkylation of the glycinate derivative **20** was promoted by 30 mol % of the C_2-symmetric chiral pentacyclic guanidine-type phase transfer catalysts **18–19** (Scheme 7.3). Interestingly, only catalyst **18a** afforded product (*R*)-**21a** in high enantioselectivity (90% *ee*) [19b]. The asymmetric alkylation proceeded using various activated and





catalyst	yield (%)	*ee* (%)
18a	55%	90% *ee*
18b	64%	13% *ee*
18c	65%	12% *ee*
19	50%	7% *ee* (*S*)

Selected examples using catalyst **18a**



(*R*)-**21b** 81%, 90% *ee*

(*R*)-**21c** 61%, 81% *ee*

(*R*)-**21d** 80%, 76% *ee*

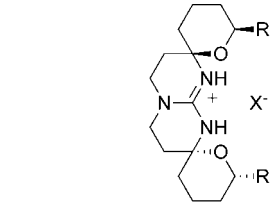
Scheme 7.3

non-activated alkylating agents, and the formation of product (*R*)-**21** with enantioselectivity in the range of 76 to 90% *ee* [19b]. The guanidine catalyst was recovered almost quantitatively after the reaction. The closed-type cavity structure and substituents on the spiro ether ring both played significant roles in this alkylation reaction.

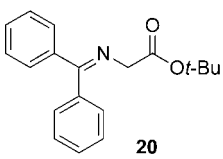
According to the transition state proposed by Nagasawa *et al.*, the catalyst forms a complex with the *Z*-enolate of Schiffs base through ionic and hydrogen-bonding interactions. In addition, the methyl groups on the spiro ether ring controls the electrophile approach.

A similar guanidinium salt **22a** was prepared by Murphy and coworkers in six steps, starting from (*R*)-3-hydroxybutyrate [20a]. Being encouraged by Nagasawa's findings on asymmetric alkylation using guanidinium salts, Murphy *et al.* synthesized C_2-symmetric guanidinium salts **22b–d**, and these catalysts were tested in the asymmetric alkylation reaction (Scheme 7.4) [20b]. Among four guanidinium salts, **22a** was highly efficient in the asymmetric benzylation of glycinate derivative **20**, and exhibited almost the same level of asymmetric induction as that obtained using Nagasawa's guanidine catalysts. The poor results using catalyst **22b** were attributed to its poor solubility in organic solvents. Of particular note, the catalyst could be recovered and recycled after anion exchange. The guanidinium salt **22a** also promoted the epoxidation of chalcone, with excellent enantioselectivity [20b].

Being inspired by Maruoka's results with the C_2-symmetric binaphthyl-derived quaternary ammonium salt [21], Lygo and colleagues designed a quaternary ammonium salt **23**, comprising conformationally flexible biphenyl units and commercially available chiral secondary amines [22]. A library of 40 quaternary ammonium salt was synthesized and evaluated for their catalytic efficiency in the asymmetric alkylation of

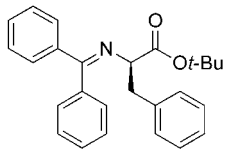


22a: R= Me, X= BF_4
22b: R= CH_2OH, X= Cl
22c: R= $CH_2OTBDMS$, X= BF_4
22d: R= $CH_2OTBDPS$, X= BF_4



20

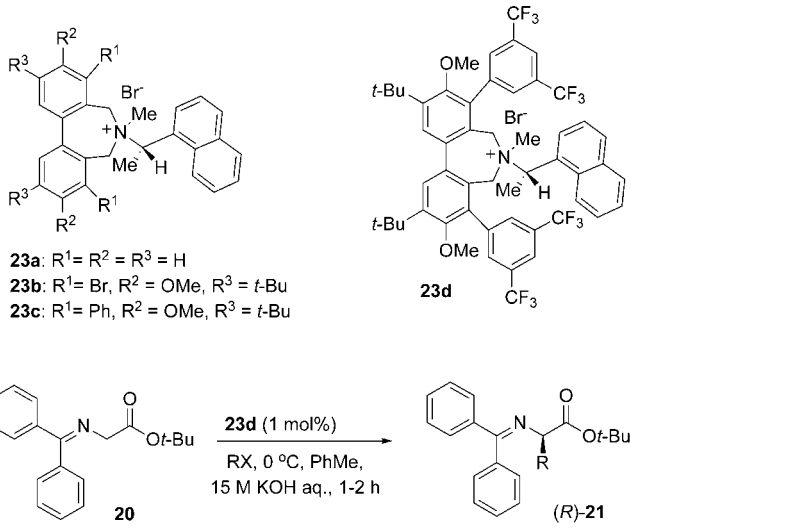
Catalyst (30 mol%)
BnBr, 0 °C-rt, CH_2Cl_2,
NaOH aq., 16 h



(*R*)-**21a**

catalyst	conversion (%)	*ee* (%)
22a	97	86
22b	15	21
22c	70	65
22d	50	74

Scheme 7.4

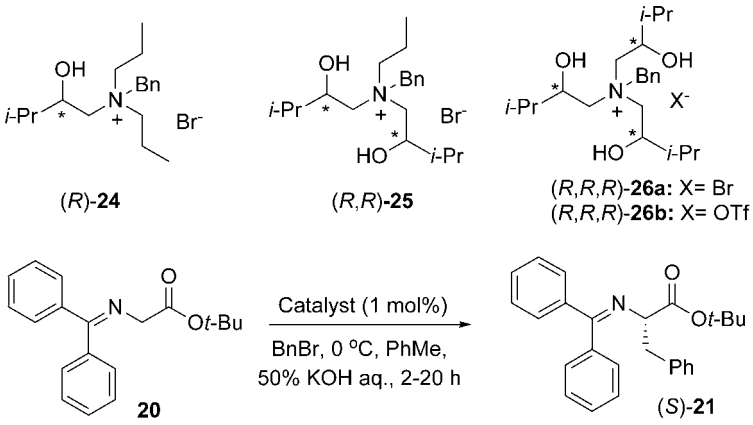


Scheme 7.5

Schiff's base ester **20** (Scheme 7.5). In general, the structure of the biphenyl unit and chiral amine both played important roles in the induction of asymmetry.

The quaternary ammonium salt **23a** with an unsubstituted biphenyl ring showed low enantioselectivity to give **21**, while **23b** ($R^1 = Br$) afforded the opposite enantiomer with the same levels of enantioselectivity to that of **23c** ($R^1 = Ph$). The most effective catalyst **23d** was then used for the asymmetric alkylation of Schiff's base **20** using various alkylating agents, and with a catalyst loading as low as 1 mol %; product (*R*)-**21** was subsequently obtained with enantioselectivity in the range of 89 to 97% *ee*. The results of these studies suggested that a C_2-symmetric structure is not essential for obtaining high enantioselectivity.

A new C_3-symmetric chiral phase-transfer catalyst that offers multipoint inteaction with a nucleophile has been described (Scheme 7.6) [23]. Thus, various quaternary ammonium salts were prepared through the ring opening of optically active epoxides, followed by quaternization of the resulting amines. Asymmetric benzylation of Schiff's base **20** in the presence of catalyst **24–26** yielded (*S*)-**21** with moderate enantioselectivity. As expected, the C_3-symmetric catalyst (*R,R,R*)-**26a** provided



catalyst	yield (%)	*ee* (%)
(*R*)-**24**	79	39
(*R*)-**25**	75	23
(*R,R,R*)-**26a**	62	55
(*R,R,R*)-**26b**	55	58

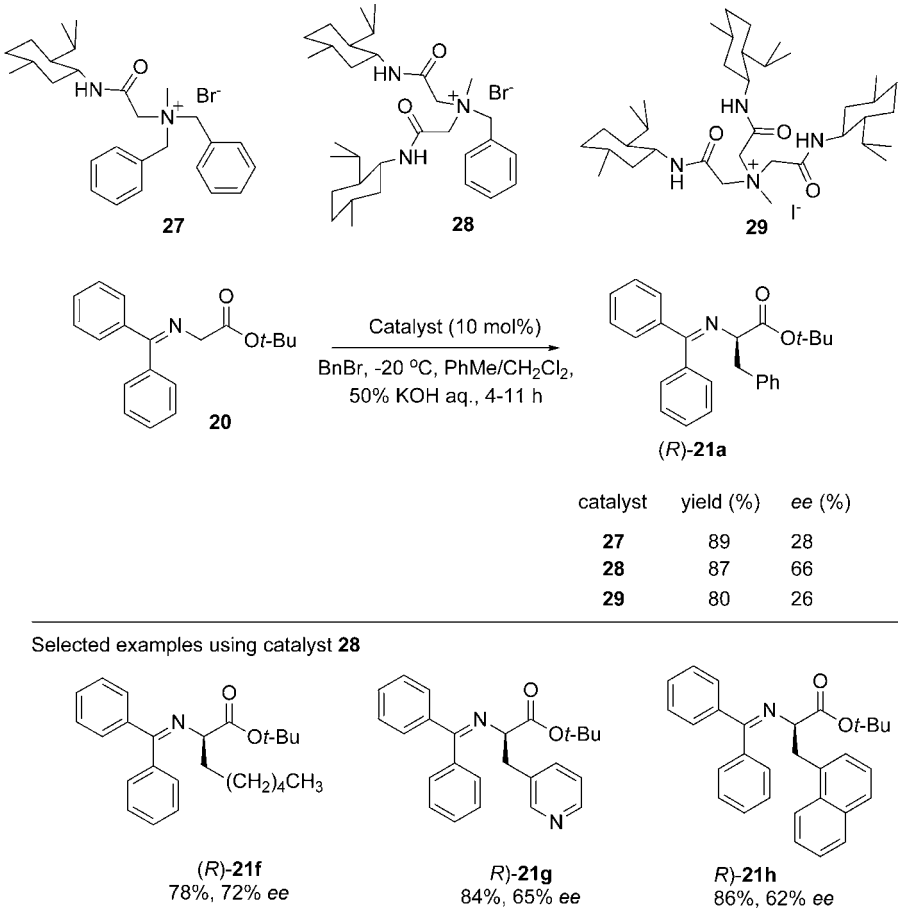
Scheme 7.6

a higher enantioselectivity than did the mono and di-chiral group-substituted phase-transfer catalysts (*R*)-**24** and (*R,R*)-**25**. A similar level of asymmetric induction (58% ee) was observed when the catalyst counteranion was exchanged for the triflate anion.

Chiral quaternary ammonium salts derived from *l*-menthol have been synthesized and applied in an asymmetric alkylation reaction to afford products in moderate enantioselectivity (Scheme 7.7) [24]. A total of nine chiral quaternary ammonium salts were prepared from *l*-menthol and tested in the asymmetric benzylation of glycinate derivative **20**. The catalysts without an amide unit afforded an almost racemic product (*R*)-**21**, while catalyst **27** with a single amide unit provided (*R*)-**21a** in 28% *ee*, suggesting a possible role for hydrogen bonding. Further screening of the catalysts identified the optimal catalyst **28** as having two *l*-menthol amide units and giving the product (*R*)-**21a** in 66% *ee*, while the use of various alkylating agents afforded products up to 72% *ee*.

The MacFarland group developed a 2,5-dimethylpyrroline ring containing tartrate-derived dicationic phase-transfer catalysts, and applied in asymmetric reactions to obtain modest enantioselectivity [25]. Further investigations identified a single-centered chiral phase-transfer catalyst derived from styrene oxide and chiral α, α-disubstituted pyrroline and piperidine that showed moderate to good (but, interestingly, reversal) enantioselectivity, as shown in Table 7.2 [26]. The chiral quaternary ammonium salts **30–32** were composed of three chiral centers that provided a good asymmetric environment for the reactive ammonium cation.

Both diastereomeric pairs of catalyst **30** and **31** were prepared in two steps, starting with a ring opening of optically pure styrene oxide with chiral amines, followed by alkylation. Interestingly, the alkylation of glycinate derivative **20** using **30a** showed a

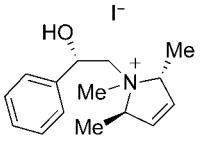


Scheme 7.7

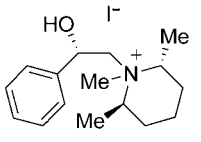
change in enantioselectivity over a period of time. The alkylation of Schiff's base with 2-methylbenzyl bromide after 10 min produced (+)-**21i** in 65% *ee* (Table 7.2, entry 1), although after 60 min (−)-**21i** with 34% *ee* was obtained (entry 2). A similar trend was observed with other catalysts **30b**, **31a** and **31b**, although this change in selectivity was not consistent for all alkyl halides (e.g., Table 7.2, entries 3 and 4). It should be noted that the catalysts **30** and **31** were found to undergo *O*-alkylation during the course of the reaction. In order to screen the effect of alkylation on the change in selectivity, the β-hydroxy group in catalyst **30a** was alkylated to provide chiral phase-transfer catalysts **32a–c** that afforded an improved – and surprisingly even larger – change in enantioselectivity (Table 7.2, entries 9–14). Moreover, this phenomenon could be suppressed by the addition of cesium bromide (30 equiv.) to the reaction mixture. It is believed that the counter anion plays a crucial role in this unusual swing in enantioselectivity.

Ramachandran and Kumar used commercially available isomannide (**33**) and isosorbide (**34**) for the synthesis of rigid bicyclic chiral quaternary ammonium

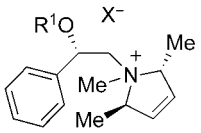
Table 7.2 Asymmetric *C*-benzylation of glycine imine **20** using chiral PTCs **30–32**.



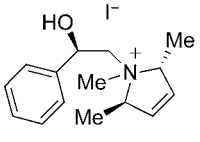
(*S*,*R*,*R*)-**30a**



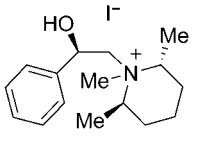
(*S*,*R*,*R*)-**31a**



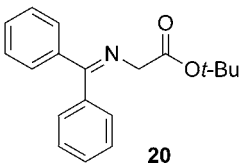
32a: R^1= Bn
32b: R^1= 2-naphthylmethyl
32c: R^1= 9-anthracenylmethyl



(*R*,*R*,*R*)-**30b**

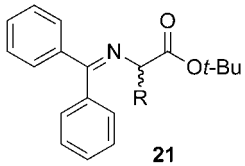


(*R*,*R*,*R*)-**31b**



20

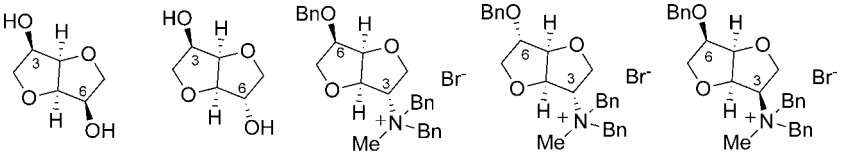
Catalyst (5 mol%)
RX, 0 °C, solvent,
CsOH, time



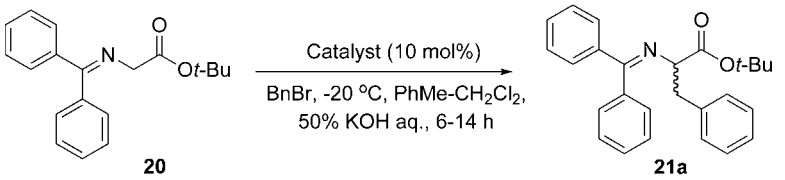
21

Entry	Catalyst	Solvent	RX	Time (min)	Product	Conversion (%)	*ee* (%)
1	**30a**	PhMe	2-(CH_3)BnBr	10	(+)-**21i**	11	65
2	**30a**	PhMe	2-(CH_3)BnBr	60	(−)-**21i**	95	34
3	**30b**	CH_2Cl_2	4-(CH_3)BnBr	10	(−)-**21j**	19	81
4	**30b**	CH_2Cl_2	4-(CH_3)BnBr	60	(−)-**21j**	68	13
5	**31a**	CH_2Cl_2	2-(CH_3)BnBr	10	(+)-**21i**	10	31
6	**31a**	CH_2Cl_2	2-(CH_3)BnBr	60	(−)-**21i**	63	23
7	**31b**	CH_2Cl_2	2-(CH_3)BnBr	10	(+)-**21i**	6	39
8	**31b**	CH_2Cl_2	2-(CH_3)BnBr	60	(−)-**21i**	58	44
9	**32a**	CH_2Cl_2	BnBr	10	(+)-**21a**	21	66
10	**32a**	CH_2Cl_2	BnBr	60	(−)-**21a**	100	51
11	**32b**	CH_2Cl_2	2-(CH_3)BnBr	10	(+)-**21i**	5	67
12	**32b**	CH_2Cl_2	2-(CH_3)BnBr	60	(−)-**21i**	63	69
13	**32c**	PhMe	2-(CH_3)BnBr	10	(−)-**21i**	4	22
14	**32c**	PhMe	2-(CH_3)BnBr	120	(+)-**21i**	60	6

salts [27]. Isomannide (**33**) has C-3 and C-6 hydroxy groups at the *endo* position, while isosorbide (**34**) possesses a C-3 hydroxy at *endo* and a C-6 hydroxy at the *exo* position. In order to screen the effects of the C-3 and C-6 positions on asymmetric induction, various quaternary ammonium salts were prepared via a series of simple transformations. These catalysts were then tested for the asymmetric alkylation of glycinate



Isomannide (**33**) | Isosorbide (**34**) | (3-*exo*, 6-*endo*) **35a** | (3-*exo*, 6-*exo*) **35b** | (3-*endo*, 6-*endo*) **35c**



20 → **21a**

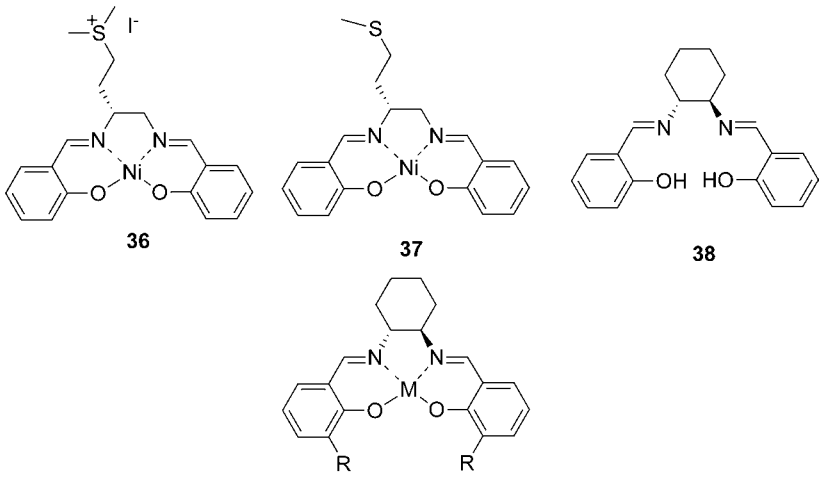
catalyst	product	yield (%)	*ee* (%)
35a	(*S*)-**21a**	83	40
35b	(*S*)-**21a**	89	14
35c	(*R*)-**21a**	90	44

Scheme 7.8

derivative **20** (Scheme 7.8). Although only moderate enantiomeric excess was obtained, some points are worthy of mention here, as the stereochemistry at C-3 was seen to control the preference of enantiomer formation, the *exo* quaternary nitrogen at C-3 favored (*S*)-**21a**, and *endo* favored (*R*)-**21a**.

Among other chiral phase-transfer catalysts, Belokon' and Kagan first described, in 1998, a novel chiral solid–liquid phase-transfer catalyst system using anions from TADDOL [28] and NOBIN [29] for the synthesis of α,α-disubstituted amino acid derivatives with enantiomeric excess up to 93%. These catalysts function as chelating agents for the sodium cation, and thus render the resulting ion-pair (formed by the corresponding carbanion and alkali ions) soluble in organic solvents. The chiral ion-pair also provides a rigid complex between the chiral ligand and substrate in the transition state of alkylation.

Subsequently, in 1999 Belokon' and North explored chiral salen–metal complexes as efficient chiral phase-transfer catalysts [30]. Analogous to TADDOL and NOBIN, chiral salen–metal complexes were expected to function by activating the ion-pair through complexation with the alkali ion. Accordingly, a series of chiral salen–metal complexes was tested for the asymmetric alkylation of benzylidene imine of alanine ester **40a** with benzyl bromide under solid–liquid phase-transfer conditions (Scheme 7.9 and Table 7.3). The initial studies using a positively charged salen–Ni (II) complex **36** did not produce any asymmetric induction (Table 7.3, entry 1), whereas a neutral complex **37** afforded encouraging results, with enantioselectivity up to 31% *ee* (entry 2). Of particular note, neither Ni nor Cu free ligand **38** could induce any asymmetric induction (entry 3) by forming an alkali metal–ligand complex similar to TADDOL or NOBIN.

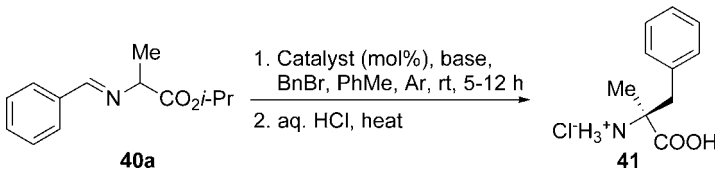


36 **37** **38**

39a: R= H, M= Ni
39b: R= *t*-Bu, M= Ni
39c: R= H, M= Cu

Scheme 7.9 Representative chiral salen-metal complexes [30].

Table 7.3 Enantioselective synthesis of α,α-dialkylamino acid derivatives using salen-Cu(II) complexes: effect of metal and base.



40a **41**

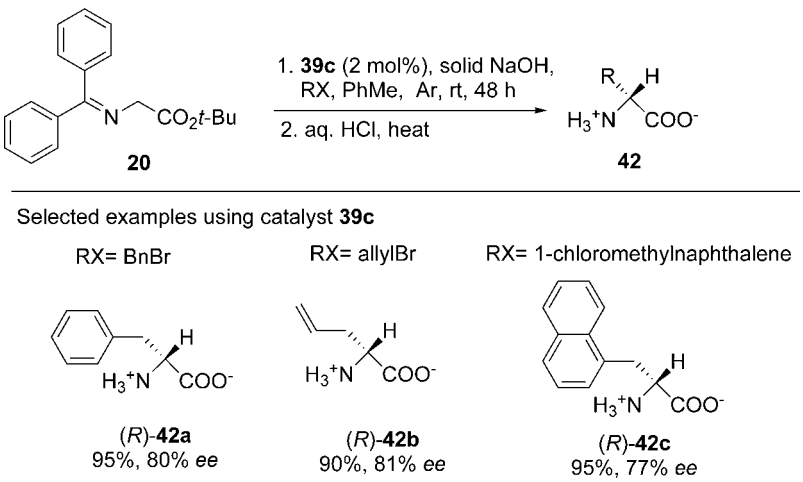
Entry	Catalyst (mol%)	Base (equiv.)	Yield (%)	*ee* (%)
1	**36** (10)	NaOH (1.5)	50	1
2	**37** (10)	NaOH (1.5)	44	31 (*R*)
3	**38** (10)	NaOH (1.2)	50	0.5
4	**39a** (10)	NaOH (1.2)	34	30 (*R*)
5	**39b** (10)	NaOH (1.2)	47	6 (*R*)
6	**39c** (10)	NaOH (1.2)	40	85 (*R*)
7	***ent*-39c** (2)	50% aq. NaOH	4	80 (*R*)
8	**39c** (10)	NaH (1.2)	82	89 (*R*)
9	***ent*-39c** (1)	NaOH (3.0)	71	92 (*S*)
10	***ent*-39c** (2)	NaOH (3.5)	91	88 (*S*)
11	***ent*-39c** (2)	LiOH (2.0)	7	0
12	***ent*-39c** (2)	KOH (2.0)	87	63 (*S*)

The salen–Ni(II) complex **39a** derived from (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane was also equally effective (Table 7.3, entry 4). In contrast to earlier reports on salen–metal complexes, where the introduction of a bulky *tert*-butyl substituent increased enantioselectivity [31], the use of complex **39b** exhibited a significant decrease in enantioselectivity (entry 5). The presence of a bulky *tert*-butyl group obstructed the chelation of alkali metal ions by phenolic oxygen atoms. A dramatic increase in selectivity could be achieved when nickel was replaced with copper, and a salen–Cu(II) complex **39c** afforded 85% *ee* (entry 6). Although screening of other bases or 50% NaOH were not advantageous, the use of 3 equiv. NaOH improved the enantiomeric excess to 92% (entry 9) and after recrystallization of α-methylphenylalanine optical purity was increased to 98% *ee*.

7.2.1.1 Substrate Scope

Chiral salen–Cu(II) complex **39c** also promoted selective monoalkylation of glycine derivative **20** to produce the corresponding α-amino acids (*R*)-**42** with enantiomeric excesses in the range of 70 to 80% (Scheme 7.10) [32]. The enantiomeric excess was not affected by reaction time.

Extensive studies have been carried out on the asymmetric alkylation of various Schiff's base esters under cinchona alkaloid-derived chiral phase-transfer catalysts. These studies revealed a significant impact of the ester moiety in glycinate or alaninate imine substrates on the enantioselectivity of the product [33]. In general, sterically bulky ester groups such as *tert*-butyl or *iso*-propyl afforded products with high enantioselectivity. *N*-benzylidine glycine or alanine methyl esters are comparatively easy to prepare on a commercial scale, and represent more suitable substrates. However, such substrates suffer from low enantioselectivity and facile hydrolysis of alkylated imines. Chiral salen–metal complex **39c** activated Schiff's base esters through a strong ion-pair interaction, and thus promoted the alkylation of readily available the sterically less bulky *N*-benzylidene alanine methyl ester to afford

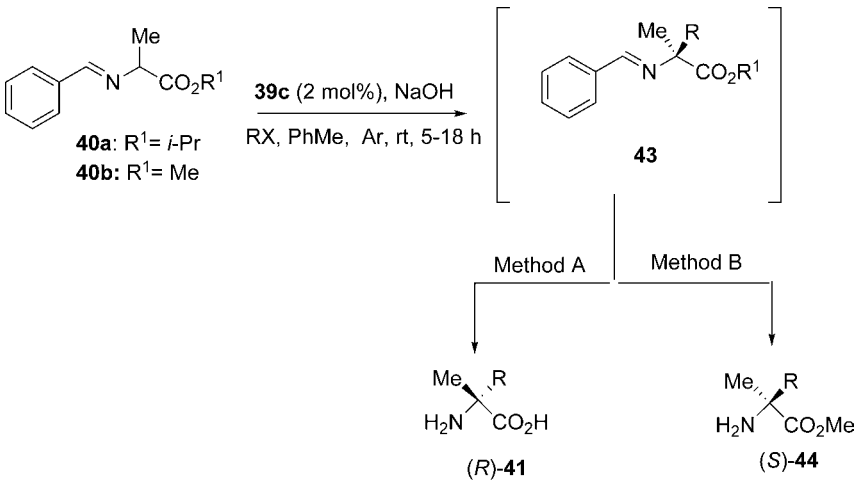


Scheme 7.10

products with high enantioselectivity. Moreover, a simple modification in the work-up procedure avoided hydrolysis of the alkylated imines. A re-esterification step was introduced after the initial alkylation reaction, and the imine was hydrolyzed using silica gel. Asymmetric alkylation of **40a** and **40b** using various alkyl halides was promoted by chiral salen–Cu(II) complex **39c** to produce corresponding α,α-disubstituted amino acids derivatives with good to excellent enantioselectivity (Table 7.4). Interestingly, sterically less bulky substrate **40b** exhibited similar levels of asymmetric induction to that of sterically demanding substrate **40a**.

The imine structure within the substrate also has a significant influence on asymmetric induction in the salen–Cu(II)-catalyzed enantioselective alkylation

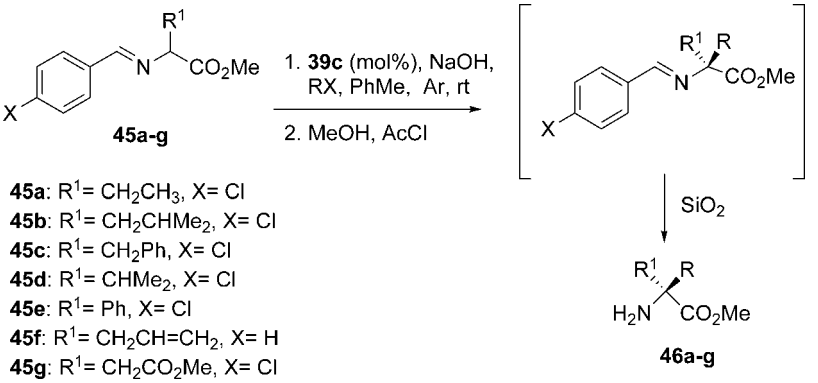
Table 7.4 α,α-Dialkylamino acid derivatives by asymmetric alkylation of imines **40a** and **40b** utilizing salen-Cu(II) complex **39c**.



Method A: 1) H_3O^+, heat
Method B: 1) MeOH, AcCl, PhMe, rt, 6 h; 2) Silica gel

Entry	Substrate	RX	Method	Product	Yield (%)	*ee* (%)	Ref.
1	**40a**	BnBr	A	**41a**	99	76	[32]
2	**40b**	BnBr	B	**44a**	91	81	[34]
3	**40b**	4-$NO_2C_6H_4CH_2Br$	B	**44b**	78	85	[34]
4	**40b**	4-$OMeC_6H_4CH_2Cl$	B	**44c**	42	60	[34]
5	**40a**	1-Chloromethylnaphthalene	A	**41b**	52	88	[32]
6	**40b**	1-Bromomethylnaphthalene	B	**44d**	85	86	[34]
7	**40b**	2-Bromomethylnaphthalene	B	**44e**	82	84	[34]
8	**40a**	Allyl bromide	A	**41c**	40	90	[32]
9	**40b**	Allyl bromide	B	**44f**	75	72	[34]

Table 7.5 Enantioselective synthesis of α,α-dialkylamino acid derivatives using **39c**: substrate scope.



45a: $R^1 = CH_2CH_3$, X= Cl
45b: $R^1 = CH_2CHMe_2$, X= Cl
45c: $R^1 = CH_2Ph$, X= Cl
45d: $R^1 = CHMe_2$, X= Cl
45e: R^1= Ph, X= Cl
45f: $R^1 = CH_2CH{=}CH_2$, X= H
45g: $R^1 = CH_2CO_2Me$, X= Cl

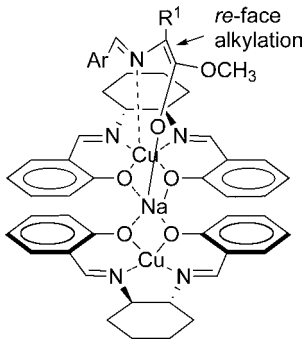
Entry	Substrate	RX	Catalyst (mol%)	Time (days)	Yield (%)	*ee* (%)
1	**45a**	BnBr	2	2	91	82
2	**45b**	BnBr	10	7	54	55
3	**45c**	Allyl-Br	25	1	68	27
4	**45d**	BnBr	10	2	0	—
5	**45e**	Allyl-Br	2	1	31	48
6	**45f**	BnBr	2	2	66	57
7	**45g**	Allyl-Br	2	1	25	17

reaction. A systematic screening of a range of aryl imines provided 4-chlorophenyl imine of alanine methyl ester as the optimal substrate, affording benzylated product in 71% yield and 92% *ee* [35]. The versatility of catalyst **39c** was evidenced by its use in the asymmetric alkylation of imines derived from various amino acids under optimized conditions (Table 7.5) [36,37].

α-Aminobutyric acid-derived imine **45a** produced a product with good enantioselectivity, although a detrimental effect upon enantioselectivity was noted when hindered substrates derived from leucine **45b**, phenylalanine **45c**, valine **45d** and aspartic acid derivative **45g** were employed (Table 7.5).

7.2.1.2 Mechanistic Investigations

Based on a positive non-linear effect observed for the alkylation of alanine and glycine substrates **40** and **20**, active species involved in these transformation are predicted to be comprising of more than one salen–Cu(II) complex **39c** [32]. Furthermore, enantioselectivity was affected by catalyst concentration, which suggested that a catalytically active dimeric form of the catalyst existed in equilibrium with catalytically inactive oligomeric and monomeric forms of the complex [36].



Scheme 7.11

A model, predicting the absolute configuration and effect of the amino acid side chain upon the enantioselectivity of alkylation, has been proposed (Scheme 7.11) [32,37].

An ion-pair derived from the substrate and solid NaOH forms a cation-assisted dimeric hydrophobic complex with catalyst **39c**, and the deprotonated substrate occupies the apical coordination site of one of the Cu(II) ions of the complexes. Alkylation proceeds preferentially on the *re*-face of the enolate to produce amino acid derivatives with high enantioselectivity. However, amino ester enolates derived from amino acids other than glycine and alanine with R^1 side chains are likely to hinder the *re*-face of enolate, resulting in a diminishing reaction rate and enantioselectivity (Table 7.5). The salen–Cu(II) complex helps to transfer the ion-pair in organic solvents, and at the same time fixes the orientation of the coordinated carbanion in the transition state which, on alkylation, releases the catalyst to continue the cycle.

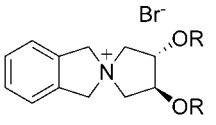
Among several chiral cyclic and acyclic diamines, (*R,R*)-cyclohexane-1,2-diamine-derived salen ligand (which can adopt the *gauche* conformation) was most effective in providing high enantioselectivity [38]. Further, the introduction of substituents at the 3, 4, 5 and 6 positions on the aromatic ring of catalyst **39c** was not advantageous, and resulted in low enantioselectivity [32,37,39]. The metal ions from first-row transition metals – particularly copper(II) and cobalt(II) – that could form square-planar complexes, produced catalytically active complexes for the asymmetric alkylation of amino ester enolates [38].

7.2.2
Michael Reaction

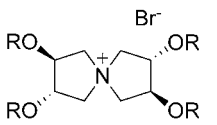
Recently, chiral phase-transfer-catalyzed asymmetric Michael addition has received much attention, and excellent enantioselectivity (up to 99% *ee*) has been reported using cinchona alkaloid-derived chiral phase-transfer catalysts [40]. Among non-cinchona alkaloid-derived chiral phase-transfer catalysts Shibasaki's tartrate derived C_2-symmetrical two-center catalyst provided a Michael adduct with up to 82% *ee* [41].

Arai and Nishida described L-tartrate-derived single-center spiro ammonium salts **47** and **48** for the asymmetric Michael addition of glycine Schiff's base [42].

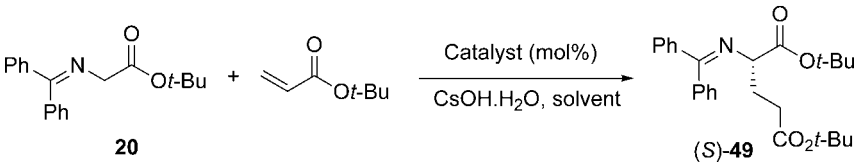
Table 7.6 Catalytic enantioselective Michael addition using L-tartrate-derived PTCs.



47a: R= H
47b: R= Bn



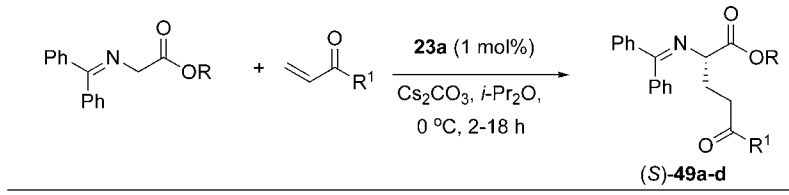
48a: R= Bn
48b: R= 4-CF_3Bn



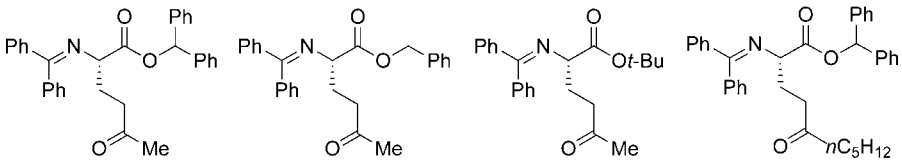
Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)	*ee* (%)
1	**47a** (5)	Et_2O	−40	33	No reaction	—
2	**47b** (5)	Et_2O	−40	33	57	22
3	**48a** (2.5)	*t*-BuOMe	−40	48	81	59
4	**48a** (10)	*t*-BuOMe	−60	70	86	73
5	**48b** (10)	*t*-BuOMe	−60	26	73	77

The chiral quaternary ammonium salt **47a** with a single tartrate moiety and free hydroxyl groups gave disappointing results for the Michael addition of Schiff's base **20** with *tert*-butyl acrylate in the presence of CsOH base. However, the benzyl-protected catalyst **47b** promoted Michael addition, and the adduct (*S*)-**49** was obtained in 57% yield, although the enantioselectivity remained low (Table 7.6, entry 2). The use of catalyst **48a**,**b** with two tartrate moieties afforded the best results at −60 °C, and Michael adduct (*S*)-**49** was obtained in good enantioselectivity up to 77% *ee* (entries 4 and 5).

A biphenyl and α-methylnaphthylamine-derived chiral quaternary ammonium salt **23d**, which was shown by Lygo to be effective for the asymmetric alkylation of Schiff's base **20**, was also effective in the Michael reaction (Scheme 7.12) [43]. Notably, the enantioselectivity was highly dependent on the reaction conditions and substrates used. The Michael reaction of imine esters such as benzhydryl and benzyl esters with α,β-unsaturated ketones under solid–liquid phase-transfer catalysis conditions afforded the Michael adduct in up to 94% *ee* and 91% *ee*, respectively, while the *tert*-butyl ester showed moderate enantioselectivity (Scheme 7.12). Interestingly, in contrast to earlier reports, acrylate [42] and acrylamides failed to undergo the Michael reaction under these optimized conditions.



Selected examples using catalyst **23a**



(*S*)-**49a** 84%, 94% *ee*

(*S*)-**49b** 94%, 91% *ee*

(*S*)-**49c** 45%, 60% *ee*

(*S*)-**49d** 60%, 94% *ee*

Scheme 7.12

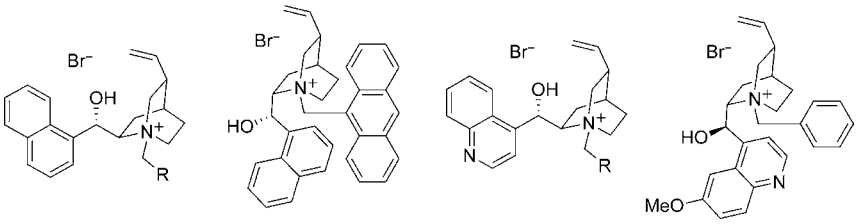
7.2.3 Epoxidation

Asymmetric epoxidation catalyzed by chiral phase-transfer catalysts is another reaction which has been extensively studied following an initial report by Wynberg [2,44]. Shioiri *et al.* further improved the enantioselective epoxidation of naphthoquinones under cinchona alkaloid-derived chiral phase-transfer catalysis [45].

Dehmlow and coworkers [17] compared the efficiency of monodeazacinchona alkaloid derivatives **14a–c** in the enantioselective epoxidation of naphthoquinone **50** with that of cinchona alkaloid-derived chiral phase-transfer catalysts **15a–c** (Table 7.7) (for comparison of the alkylation reaction, see Table 7.1). Interestingly, the non-natural cinchona alkaloid analogues **14a–c** afforded better results than natural cinchona alkaloids **15a–c**. The deazacinchonine derivatives **14a**,**b** produced epoxidation product **51** in higher enantioselectivity than the related cinchona alkaloids **15a**,**b**. Of note, catalyst **14c**, which possessed a bulky 9-anthracenylmethyl substituent on the quaternary nitrogen, afforded the highest enantioselectivity (84% *ee*).

The group of Aggarwal reported striking results in the epoxidation of olefin substrates catalyzed by simple chiral amines using Oxone as oxidant [46]. A significant asymmetric induction was observed in this process, particularly when pyrrolidines were used as chiral amines. Originally, the epoxidation of alkenes catalyzed by chiral amines was believed to involve the amine radical cation. However, subsequent studies to improve the reproducibility of the amine-catalyzed epoxidation reaction led to protonated chiral amines **53** and **54** being identified as the active species, with a dual role of phase-transfer catalysis and activation of the oxidant [47]. The protonated chiral amines not only gave reproducible results but also improved the enantioselectivity of the epoxidation product (Table 7.8). Notably, a low temperature (−10 °C)

Table 7.7 Asymmetric epoxidation using monodeazacinchona analogues **14a–c** and natural cinchona alkaloids **15a–c**.

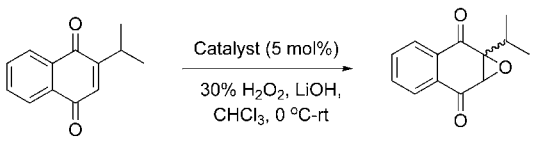


14a: R= Ph
14b: R= 4-$CF_3C_6H_4$

14c

15a: R= Ph
15b: R= 4-$CF_3C_6H_4$

15c



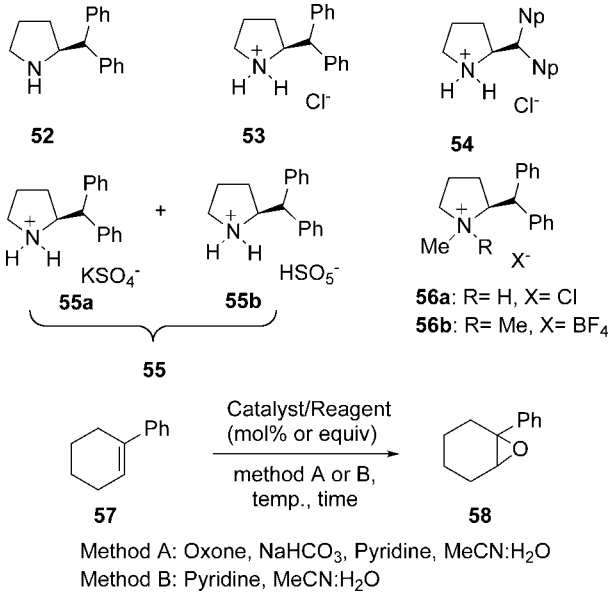
50 **51**

Entry	Catalyst	Yield (%)	*ee* (%)
1	**14a**	62	50
2	**14b**	58	66
3	**14c**	75	84
4	**15a**	80	42
5	**15b**	92	55
6	**15c**	69	39

proved to be advantageous by producing a slight improvement in enantioselectivity, and the chiral amine was recovered in 90% yield. Of note, a complex formed between Oxone and the chiral amine at −10 °C was isolated and characterized as a mixture of **55a** (40%) and **55b** (60%). The isolated mixture of complex **55** also promoted epoxidation with the same efficiency, and an identical enantioselectivity was obtained (Table 7.8, entry 5). Thus, it was believed that the chiral amine **52**, protonated amines **53** and **54** or isolated complex **55** promoted the reaction with the same key oxidant, namely ammonium salt **55b**. Interestingly, both the enantioselectivity and reactivity were decreased when tertiary **56a** (5% *ee*) and quaternary **56b** (0% *ee*) ammonium salts derived from pyrrolidine were used as catalysts. Based on these results, it is most likely that protonated chiral amines have a dual role, acting as the phase-transfer catalyst and also activating the oxidant persulfate anion for oxygen transfer through hydrogen bonding.

Aggarwal *et al.* have proposed a catalytic cycle for asymmetric epoxidation of olefins by chiral amines (Scheme 7.13), which involves the initial formation of ammonium

Table 7.8 Asymmetric epoxidation of 1-phenylcyclohexene utilizing protonated ammonium salts.

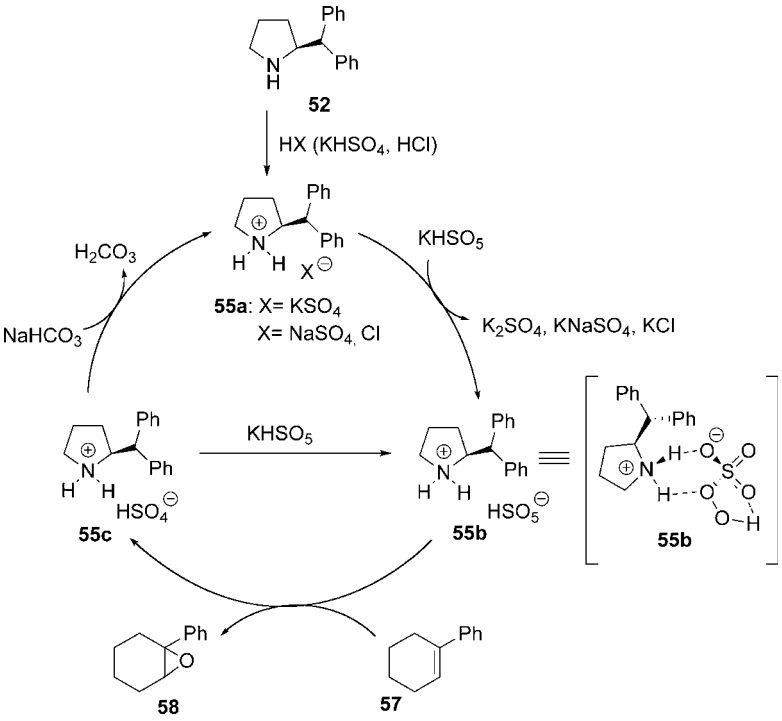


Entry	Catalyst/reagent (mol% or equiv)	Method	Temp. (°C)	Time (min)	Yield (%)	*ee* (%)
1	**52** (10 mol %)	A	r.t.	30	87–99	32–38
2	**53** (10 mol %)	A	r.t.	20	93	46
3	**54** (10 mol %)	A	r.t.	60	89	59
4	**54** (10 mol %)	A	− 10	120	49	66
5	**55** (1.8 equiv.)	B	r.t.	30	70	46
6	**56a**	A	r.t.		58	5
7	**56b**	A	r.t.		13	0

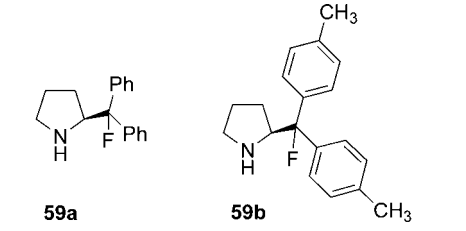
salt **55a** which, upon exchange with peroxymonosulfate, provides the catalytically active species **55b**. The oxygen transfer to olefin gives **55c**, which is converted into active species **55b** via either an exchange with persulfate or by reaction with $NaHCO_3$ to continue the catalytic cycle.

These studies were expanded by Yang and coworkers [48], who uses fluorinated chiral pyrrolidine as catalysts, such that the epoxidation of 1-phenylcyclohexene was achieved with an enantioselectivity of up to 61% *ee* (Scheme 7.14).

In contrast to the method of Aggarwal and colleagues, Yang *et al*, used lesser amounts of $NaHCO_3$ and the reaction was performed without pyridine, thus maintaining slight acidic conditions; consequently, the free amine was readily converted into the ammonium salt necessary for epoxidation (Scheme 7.14). Several chiral secondary amines with sterically demanding groups at position 2 of the



Scheme 7.13



catalyst	condition	yield (%)	*ee* (%)
59a	2 h, rt	87	50
59b	2 h, rt	76	52
59b	4 h, -20 °C	92	61

Scheme 7.14

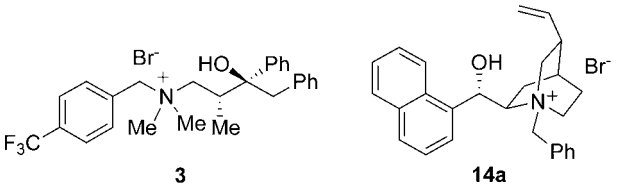
pyrrolidines were synthesized and tested for asymmetric epoxidation, though no significant improvement in enantioselectivity was noted. Experimental evidence has been provided for the role of the ammonium salt as a phase-transfer catalyst. The epoxidation of 1-phenylcyclohexene under heterogeneous conditions and using only amine catalyst **59a** afforded a low conversion (22%), whereas a combination of amine **59a** and 18-crown-6 led to a significant improvement in conversion (53%).

7.2.4
Hydroxylation

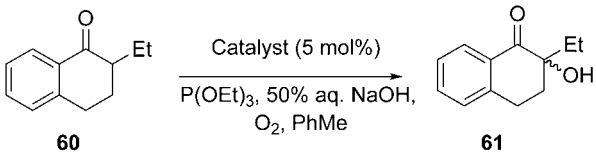
Dehmlow and coworkers used quaternary ammonium salt **3** [8d] for the peroxidative hydroxylation of 2-ethyl-1-tetralone (Scheme 7.15), which was originally introduced by Shioiri *et al.* [49].

The chiral phase-transfer catalyst **3** afforded product **61** in 49% *ee*. The same group studied this reaction further by employing monodeazacinchona derivatives **14a–c** [17]. The newly prepared non-natural analogues of cinchona alkaloids effectively promoted the hydroxylation reaction, although the enantioselectivity was lower than with natural cinchona alkaloid-derived chiral phase-transfer catalysts (Scheme 7.15).

Neutral cyclodextrins have been used as chiral phase-transfer catalysts for an interesting inverse phase-transfer catalysis reaction [50]. The Markovnikov hydration of the double bond by an oxymercuration-demercuration reaction has been demonstrated in the presence of cyclodextrins as chiral phase-transfer catalysts to obtain products in low to moderate enantioselectivity (Scheme 7.16). The mercuric salts are water-soluble, and remain in the aqueous phase, whereas the neutral alkenes prefer an organic phase. A neutral cyclodextrin helps to bring the alkenes into the aqueous phase in a biphasic reaction, and also provides the necessary asymmetric environment.



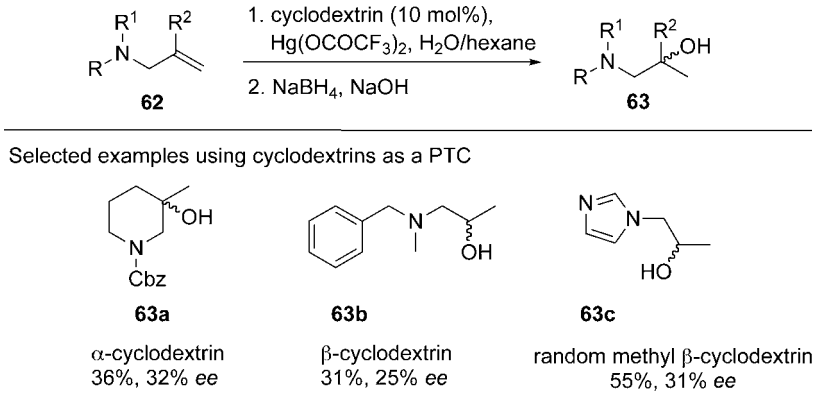
3 **14a**



60 **61**

catalyst	yield (%)	*ee* (%)	ref.
3	76	49	[8d]
14a	60	50	[17]

Scheme 7.15



Scheme 7.16

Various allylic amines and protected allylic alcohols were tested using different cyclodextrins. Although only low to moderate enantioselectivity was obtained, the method demonstrated for the first time an enantioselective inverse phase-transfer catalysis hydration reaction *via* an oxymercuration–demercuration process.

7.3 Conclusions

Chiral phase-transfer catalysis represents a very attractive and useful approach in the area of asymmetric synthesis. This chapter summarizes the development of chiral phase-transfer catalysts other than the well-known natural cinchona alkaloids, spiro quaternary ammonium salts, two-center quaternary ammonium salt, crown ethers and TADDOL or NOBIN. Considerable effort and contributions have been made to this area, leading in turn to the development of some highly efficient catalysts. Of note, a chiral pentacyclic C_2-symmetric guanidine-type phase-transfer catalyst described by Nagasawa, namely a chiral quaternary ammonium salt comprising a conformationally flexible biphenyl unit by Lygo and salen-Cu(II) complex, promoted asymmetric reactions which afforded products with high enantioselectivity. Some of the chiral catalysts described here have exhibited moderate to good enantioselectivity, and provide valuable information for the future development of efficient chiral phase-transfer catalysts.

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8
Crown Ethers, Taddol, Nobin and Metal(salen) Complexes as Chiral Phase-Transfer Catalysts for Asymmetric Synthesis

Michael North

8.1
Introduction

Asymmetric phase-transfer catalysis [1] is the enhancement of the rate of – and simultaneous induction of asymmetry in – a reaction between chemical species located in different phases by the addition of a small quantity of a phase-transfer catalyst. The catalyst extracts one of the reactants across the interface (usually liquid–liquid or solid–liquid) into the other phase so that the reaction proceeds more rapidly than in the absence of the catalyst. Phase-transfer catalysis (both achiral [2] and chiral [3]) has historically been dominated by the use of quaternary ammonium salts as the catalyst to generate a cation which is soluble in organic solvents. Only recently has the use of chiral metal complexes as asymmetric phase-transfer catalysts been developed [4]. Although this can most obviously be achieved by exploiting the well-known metal-complexing abilities of crown ethers, it has also been demonstrated that other catalysts containing two appropriately located heteroatoms can coordinate to metal ions and increase their solubility in organic solvents. The use of metal ions in asymmetric phase-transfer catalysis is attractive as the ability of metals to fix the relative orientation of chiral ligands and substrates in the coordination sphere of the complex can be exploited to induce asymmetric induction in the transition state of the reaction.

Metal-based asymmetric phase-transfer catalysts have mainly been used to catalyze two carbon–carbon bond-forming reactions: (1) the asymmetric alkylation of amino acid-derived enolates; and (2) Darzens condensations [5]. The alkylation of prochiral glycine or alanine derivatives [3] is a popular and successful strategy for the preparation of acyclic α-amino acids and α-methyl-α-amino acids respectively (Scheme 8.1). In order to facilitate the generation of these enolates and to protect the amine substituent, an imine moiety is used to increase the acidity of the α-hydrogens, and therefore allow the use of relatively mild bases (such as metal hydroxides) to achieve the alkylation. In the case of a prochiral glycine-derived imine (Scheme 8.1: $R^3 = H$), if monoalkylation is desired, the new chiral methine group

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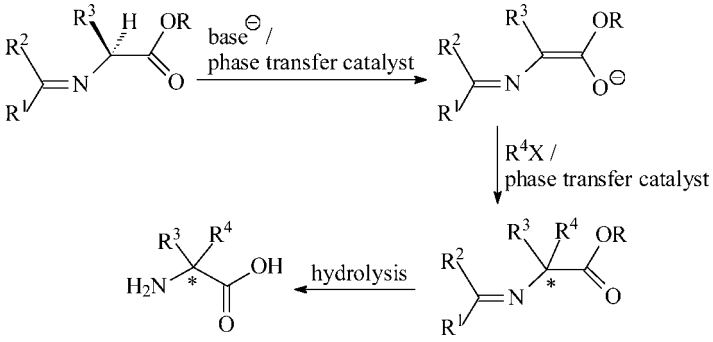
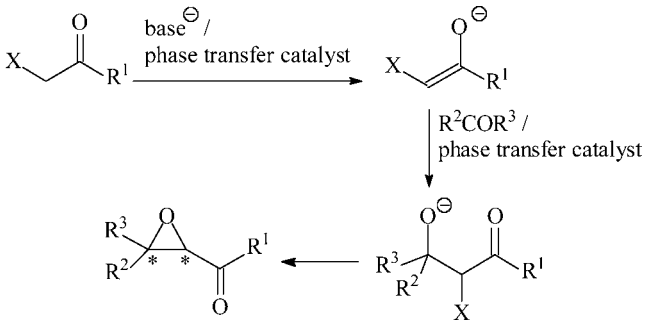


Scheme 8.1 Asymmetric synthesis of amino acid derivatives.

formed should not racemize under the reaction conditions. This is achievable since, after the first alkylation, the methine of the product is less acidic than the methylene of the starting substrate, thus avoiding a second deprotonation and a further alkylation [3]. In addition to simple alkylations, Michael additions of the enolates to α,β-unsaturated carbonyl compounds can also be induced by phase-transfer catalysts, thus giving access to functionalized amino acids.

Scheme 8.1 also illustrates an important feature of asymmetric phase-transfer catalysis, namely that the catalyst is involved in two different steps of the mechanism. Thus, the rate of reaction increases because the catalyst accelerates the substrate deprotonation step, but the asymmetric induction occurs during the subsequent enolate alkylation step.

Whilst simple alkylations of enolates and Michael additions have been successfully catalyzed by phase-transfer catalysts, aldol-type processes have proved more problematic. This difficulty is due largely o the reversible nature of the aldol reaction, resulting in the formation of a thermodynamically more stable aldol product rather than the kinetically favored product. However, by trapping the initial aldol product as soon as it is formed, asymmetric aldol-type reactions can be carried out under phase-transfer catalysis. This is the basis of the Darzens condensation (Scheme 8.2), in which the phase-transfer catalyst first induces the deprotonation of an α-halo



Scheme 8.2 Asymmetric Darzens condensation.

carbonyl compound to form a chiral enolate which undergoes an aldol reaction followed by intramolecular substitution, leading to the formation of an epoxide-containing product [5]. This process results in the formation of two new stereocenters, and both the relative and absolute configuration of these can be controlled by the catalyst and reaction conditions.

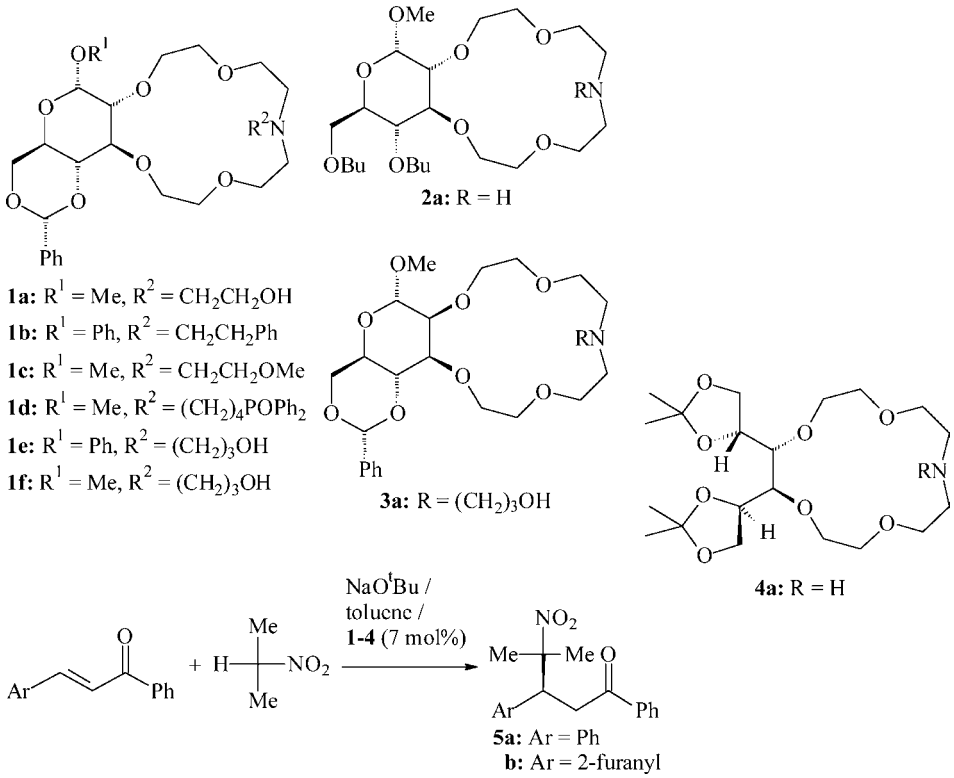
In the following sections, progress made in asymmetric phase-transfer catalysis using chiral crown ethers, taddolates, Nobin and metal(salen) complexes is surveyed. Each section is further subdivided according to the reaction being catalyzed.

8.2
Crown Ethers as Chiral Phase-Transfer Catalysts

The use of chiral crown ethers as asymmetric phase-transfer catalysts is largely due to the studies of Bakó and Tõke [6], as discussed below. Interestingly, chiral crown ethers have not been widely used for the synthesis of amino acid derivatives, but have been shown to be effective catalysts for asymmetric Michael additions of nitro-alkane enolates, for Darzens condensations, and for asymmetric epoxidations of α,β-unsaturated carbonyl compounds.

8.2.1
Use of Crown Ethers in Asymmetric Michael Additions

In 1997, Bakó and Tõke first reported the use of sugar-derived aza-crown ethers **1** as asymmetric phase-transfer catalysts for the addition of 2-nitropropane to chalcone under solid–liquid phase-transfer conditions (Scheme 8.3) [6]. A range of catalysts **1** with R^1=Me and various substituents on the nitrogen atom was tested, and Michael adduct **5a** was obtained with up to 60% enantiomeric excess (ee) in favor of the (*S*)-enantiomer from catalyst **1a**, by the use of sodium *tert*-butoxide as the base. In a subsequent communication [7], these authors showed that catalyst **1b** was more enantioselective, giving product **5a** with up to 82% *ee*, though a later full report revealed that the chemical yield of product **5a** was only 18% under these reaction conditions [8]. The *O*-methylated version of catalyst **1a** (i.e., **1c**) was subsequently shown to be a more effective catalyst for this reaction, giving compound **5a** with 87% *ee* and in 45% yield [9]. In the same report, the authors showed that the diastereomeric crown ethers with a *cis*-fusion between the two six-membered rings were less enantioselective phase-transfer catalysts. In a further study, Bakó and Tõke prepared a series of crown ethers **1** with a diphenylphosphinoxido-alkyl group on the nitrogen atom [10]. The most enantioselective of these was compound **1d**, which catalyzed the reaction shown in Scheme 8.3 to give Michael adduct **5a** in 43% yield and with 94% *ee*. The corresponding addition reaction to 3-fur-2-yl-1-phenyl-propenone occurred in 56% yield and gave compound **5b** with 80% *ee* under the same conditions. The bicyclic structure formed by the benzylidene protecting group is not essential for the enantioselectivity shown by this class of catalysts. Thus, crown ethers of structure **2** were also found to catalyze the formation of compound **5a** under the

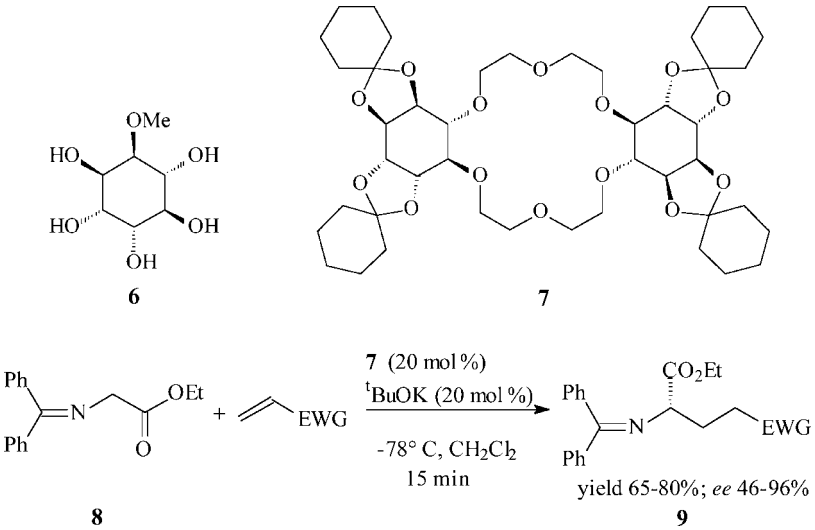


Scheme 8.3 Crown ether-induced asymmetric Michael addition of 2-nitropropane to chalcones.

conditions shown in Scheme 8.3. Interestingly however, in this case, the *N*-unprotected compound **2a** was found to display the highest enantioselectivity, generating compound **5a** in 82% yield and with 90% *ee* [11].

Bakó later prepared mannose-derived crown ethers **3** in which the macrocycle and six-membered ring are *cis*-fused [12]. Crown ethers **3** were also found to be highly enantioselective phase-transfer catalysts, and compound **3a** catalyzed the asymmetric synthesis of compound **5a** in 37% yield and with 92% *ee* in favor of the (*S*)-enantiomer. In contrast, crown ethers **4** – which lack a fused ring junction – were found to be relatively poor asymmetric phase-transfer catalysts for the reaction shown in Scheme 8.3. The best results in this case were also obtained with the *N*-unsubstituted compound **4a**, which gave compound **5a** in 38% yield and with just 67% *ee* [13].

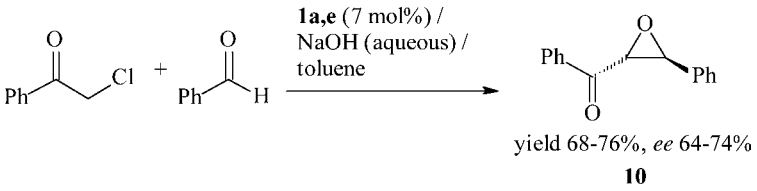
Akiyama's group employed naturally occurring L-quebrachitol **6** to prepare the C_2-symmetrical 18-membered chiral crown ether **7** [14]. Compound **7** was found to be an active catalyst for the enantioselective Michael additions of glycine enolates. Thus, deprotonation of ester **8** using potassium *tert*-butoxide in dichloromethane (DCM) in the presence of crown ether **7** (20 mol %), followed by addition of a Michael acceptor, gave amino-acid derivatives **9** with up to 96% *ee*, as shown in Scheme 8.4.



Scheme 8.4 Crown ether-induced asymmetric Michael addition of a glycine enolate.

8.2.2
Use of Crown Ethers in Darzens Condensations

In their groundbreaking 1997 report [6], Bakó and Tõke also reported the use of crown ethers **1** as asymmetric phase-transfer catalysts for the Darzens condensation between phenacyl chloride and benzaldehyde under liquid–liquid phase-transfer conditions using aqueous sodium hydroxide as base and toluene as the organic solvent (Scheme 8.5). Crown ether **1a** was again found to give the best result, producing the (2*R*,3*S*)-isomer of epoxide **10** in 76% yield and with 64% *ee* when the reaction was carried out at −20 °C. In a subsequent study [7,8], a wider range of crown ethers was investigated and compound **1e** was found to form epoxide **10** in 68% yield and with 74% *ee*, even when the reaction was carried out at room temperature. The corresponding *O*-methylated crown ether **1f** was also an effective catalyst for this Darzens condensation, and its use with substituted benzaldehydes has been reported [9]. However, the enantioselectivities were very variable in this case (range 12 to 72%). The diastereomeric crown ethers **3** were also investigated as catalysts for the Darzens condensation [12], but in contrast to the results obtained for alkylation

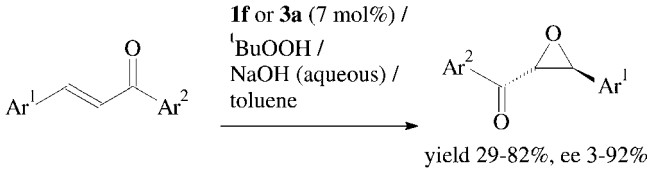


Scheme 8.5 Crown ether-catalyzed Darzens condensation.

reactions (see Section 8.1), crown ether **3a** was found to be less enantioselective than crown ethers **1**, giving epoxide **10** with just 45% *ee*.

8.2.3
Use of Crown Ethers in Asymmetric Epoxidations

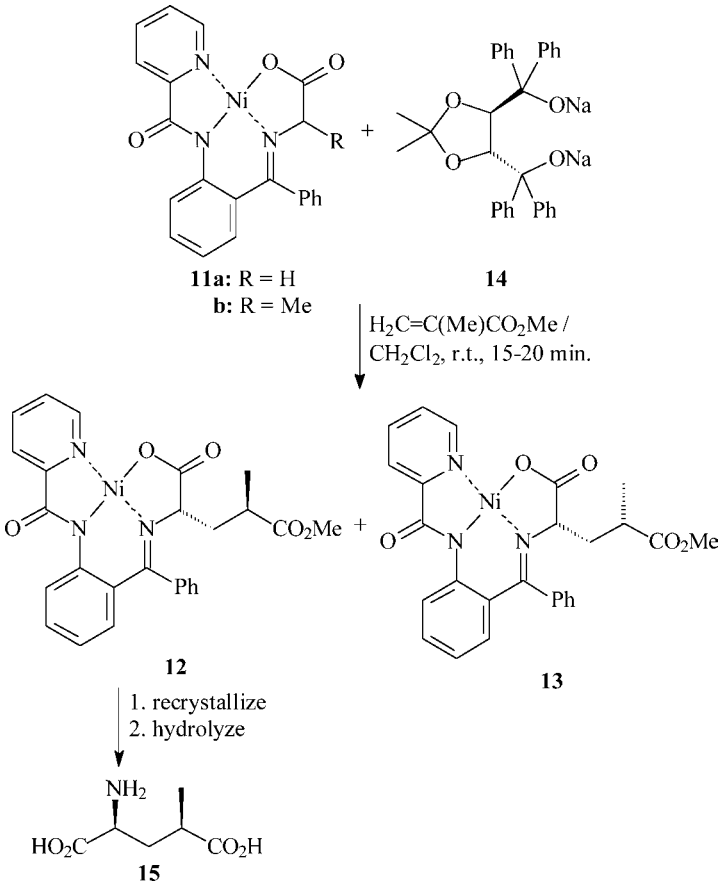
An alternative method for the asymmetric synthesis of epoxides employing phase-transfer catalysis is the asymmetric epoxidation of alkenes. Bakó and Tõke studied the use of crown ethers **1** and **3** as chiral phase-transfer catalysts for the asymmetric epoxidation of chalcones under liquid–liquid phase-transfer conditions with *tert*-butyl hydroperoxide as the oxidizing agent, as shown in Scheme 8.6 [15,16]. Crown ether **1f** was again found to be the most enantioselective catalyst, converting chalcone into (2*R*,3*S*)-epoxide **10** with 92% *ee* after a reaction time of 1 h at 5 °C. However, the process again lacks generality as other chalcones gave epoxides with ee-values of 3% to 82%. The diastereomeric crown ethers derived from mannose were also catalytically active in the epoxidation of chalcone, and crown ether **3a** gave epoxide **10** with 82% *ee* and 47% yield [13,15]. Other chalcones again gave variable results, with enantioselectivities of 32% to 82% reported for substrates in which Ar^1 and Ar^2 were varied (Scheme 8.6).



Scheme 8.6 Crown ether-catalyzed asymmetric epoxidation.

8.3
Use of Taddolates as Chiral Phase-Transfer Catalysts

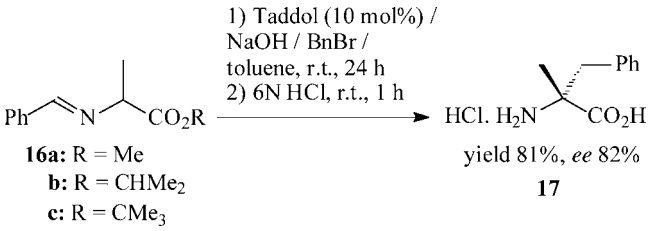
Taddol has been widely used as a chiral auxiliary or chiral ligand in asymmetric catalysis [17], and in 1997 Belokon' first showed that it could also function as an effective solid–liquid phase-transfer catalyst [18]. The initial reaction studied by Belokon' was the asymmetric Michael addition of nickel complex **11a** to methyl methacrylate to give γ-methyl glutamate precursors **12** and **13** (Scheme 8.7). It was found that only the disodium salt of Taddol **14** acted as a catalyst, and both the enantio- and diastereoselectivity were modest [20% *ee* and 65% diastereomeric excess (*de*) in favor of **12** when 10 mol % of Taddol was used]. The enantioselectivity could be increased (to 28%) by using a stoichiometric amount of Taddol, but the diastereoselectivity decreased (to 40%) under these conditions due to deprotonation of the remaining acidic proton in products **12** and **13**. Nevertheless, diastereomers **12** and **13** could be separated and the ee-value of complex **12** increased to >85% by recrystallization, thus providing enantiomerically enriched (2*S*, 4*R*)-γ-methyl glutamic acid **15**.



Scheme 8.7 Taddol-catalyzed asymmetric synthesis of γ-methyl glutamic acid **15**.

Whilst the use of Taddol as an asymmetric phase-transfer catalyst for asymmetric Michael reactions was only moderately successful, it was much more enantioselective in catalyzing alkylation reactions. For this study, Belokon' and Kagan employed alanine derivatives **11b** and **16a–c** as substrates, and investigated their alkylation with benzyl bromide under solid–liquid phase-transfer conditions in the presence of 10 mol % of Taddol to form α-methyl phenylalanine, as shown in Scheme 8.8. The best results were obtained using the isopropyl ester of *N*-benzylidene alanine **16b** as substrate and sodium hydroxide as the base. Under these conditions, (*R*)-α-methyl phenylalanine **17** could be obtained in 81% yield and with 82% *ee* [19]. Under the same reaction conditions, substrate **16b** reacted with allyl bromide to give (*R*)-α-methyl allylglycine in 89% yield and with 69% *ee*, and with (1-naphthyl)methyl chloride to give (*R*)-α-methyl (1-naphthyl)alanine in 86% yield and with 71% *ee* [20].

The nature of the metal ion within the base was critical to the enantioselectivity observed in these reactions, since whilst both sodium hydride and sodium hydroxide

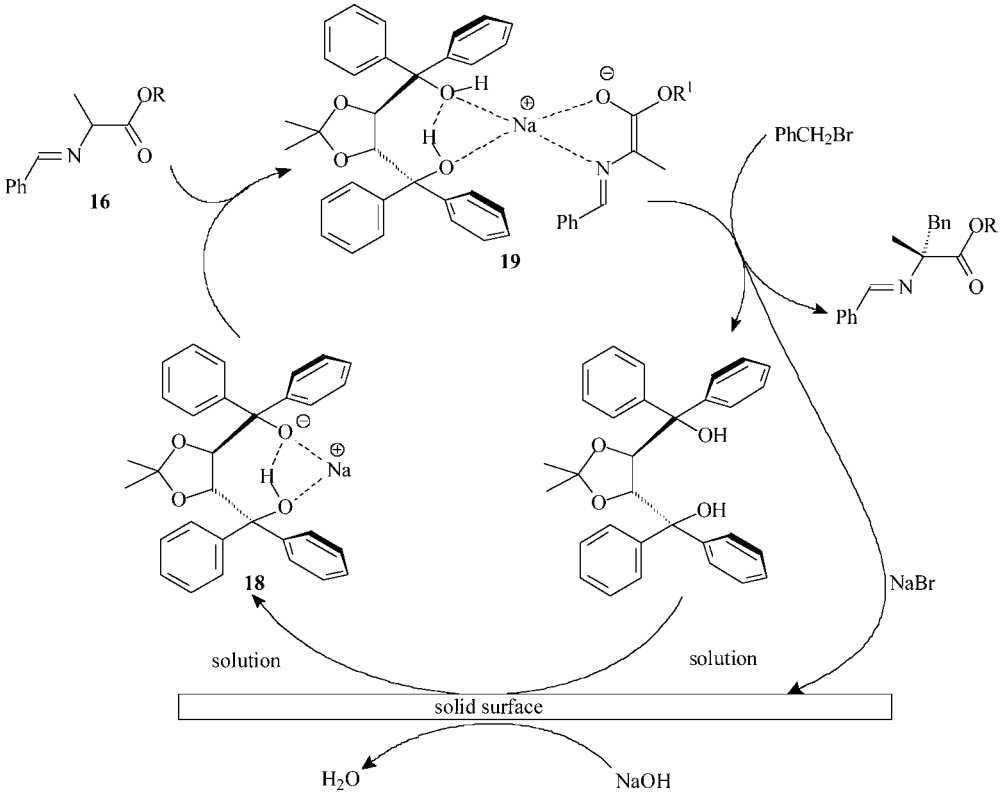


Scheme 8.8 Taddol-catalyzed asymmetric alkylation of alanine derivatives.

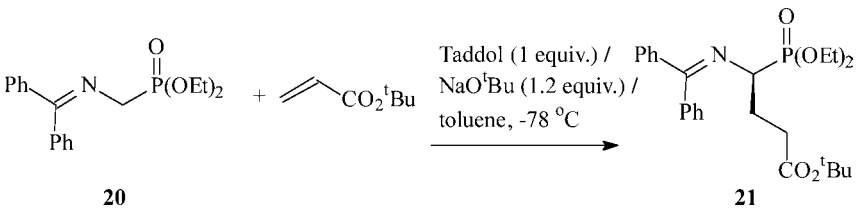
gave highly enantioselective reactions, potassium hydroxide gave product **17** with only 24% *ee*, cesium hydroxide gave the racemic product, and use of lithium hydroxide resulted in no reaction occurring. The nature of the ester also had an influence on the enantioselectivity, though this was less marked. Thus, whilst substrate **16a** failed to react in the presence of sodium hydroxide (presumably due to hydrolysis of the ester), in the presence of sodium hydride it gave product **17** with 70% *ee*. Similarly, substrate **16c** reacted with either sodium hydroxide or sodium hydride to give compound **17** with 38–40% *ee*.

In a subsequent study, it was found that changing the imine unit within substrates **16** had no effect on the asymmetric induction, and that only non-polar solvents (toluene or hexane) gave high levels of asymmetric induction [21]. However, by changing the alkylating agent from benzyl bromide to benzyl chloride, the enantiomeric excess of product **17** could be increased to 93%. The effect of varying the structure of the Taddol catalyst was also investigated. It was found that both *O*-monoalkylated and *O,O′*-dialkylated derivatives displayed negligible asymmetric induction, and changing the phenyl rings of the Taddol unit to hydrogens or naphthyl rings was also detrimental to the asymmetric induction. On the basis of this information, the authors outlined a possible reaction mechanism to explain the phase-transfer ability of Taddol (Scheme 8.9). In this mechanism, Taddol is mono-deprotonated by the solid sodium hydroxide to give a soluble mono-sodium salt **18**, the structure of which is stabilized by an intramolecular hydrogen bond. Compound **18** acts as a base to deprotonate substrate **16** and form a complex **19** in which both the Taddol and the enolate are coordinated to the same sodium ion. Alkylation of the coordinated enolate from its less-hindered face generates the alkylated product and reforms the Taddol along with sodium bromide, which can be precipitated back onto the solid surface. It is believed that both sodium complexes **18** and **19** are soluble in organic solvents, and thus that the two alcohols of Taddol perform a similar role to the heteroatoms in a crown ether in generating an organic solvent-soluble sodium complex.

The use of Taddol as an asymmetric phase-transfer catalyst has been adopted by other research groups. For example, Jaszay has used Taddol for Michael additions to α-aminophosphonate derivative **20**, as shown Scheme 8.10 [22]. A range of Taddol derivatives was investigated, but the best results were again obtained with the same catalyst employed by Belokon' and Kagan. Thus, phosphoglutamic acid derivative **21** was obtained in 95% yield and with 72% *ee* when *tert*-butyl acrylate was employed as the Michael acceptor.

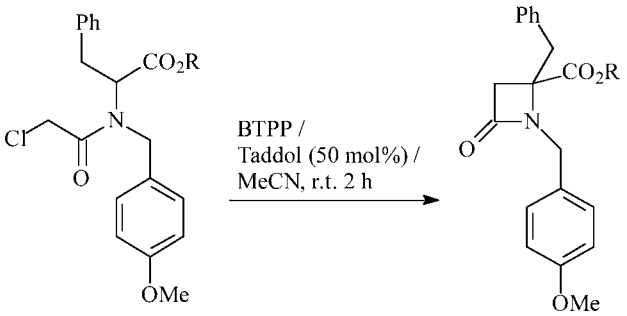


Scheme 8.9 Proposed mechanism for Taddol-catalyzed alkylation reactions.



Scheme 8.10 Synthesis of phosphoglutamic acid derivatives.

The intramolecular alkylation of the enolate derived from phenylalanine derivatives **22a**,**b** to form β-lactams **23a**,**b** has also been achieved using Taddol as a chiral phase-transfer catalyst (Scheme 8.11) [23]. In this process, the stereocenter within enantiomerically pure starting material **22** is first destroyed and then regenerated, so that the Taddol acts as a chiral memory relay. Taddol was found to be superior to other phase-transfer catalysts (cinchona alkaloids, binol, etc.) in this reaction, and under optimal conditions (50 mol % Taddol in acetonitrile with BTPP as base), β-lactam **23b** could be obtained with 82% *ee*. The use of other amino acids was also studied, and the



22a: R = Me
b: R = ^{t}Bu

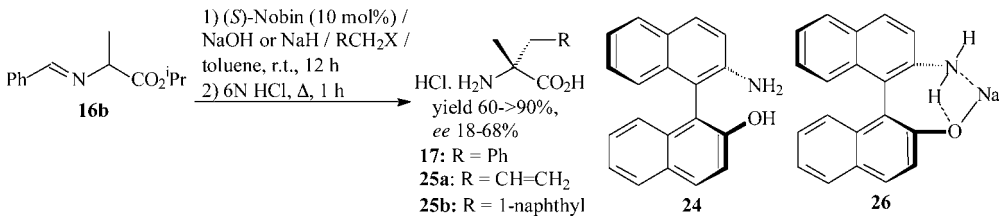
23a: R = Me
b: R = ^{t}Bu

Scheme 8.11 Synthesis of β-lactams.

presence of an aromatic ring within the side chain of the amino acid residue was found to be essential for efficient asymmetric transfer. Interestingly, the stereochemistry of the starting material rather than that of the Taddol determined the stereochemistry of the product. Thus, use of (*S*)-**22a** gave the (*S*)-enantiomer of β-lactam **23a** with 62% *ee*, whereas the same reaction carried out on (*R*)-**22a** gave (*R*)-**23a**, also with 62% *ee*. The use of racemic **22a** gave essentially racemic product, which implies that both the Taddol and unreacted starting material are involved in the enantiodetermining transition state.

8.4
Use of Nobin and Related Species as Asymmetric Phase-Transfer Catalysts

Following on from the success achieved using Taddol as an asymmetric phase-transfer agent (see Section 8.3), Belokon' and Kagan reasoned that other organic molecules containing two heteroatoms, appropriately located to coordinate to a metal, and held in a rigid environment by an intramolecular hydrogen bond, should be able to function as asymmetric phase-transfer catalysts. This hypothesis was confirmed in 1999 by the discovery that Nobin 24 would function as an asymmetric phase-transfer catalyst for the alkylation of alanine derivative **16b**, as shown in Scheme 8.12 [21,24].



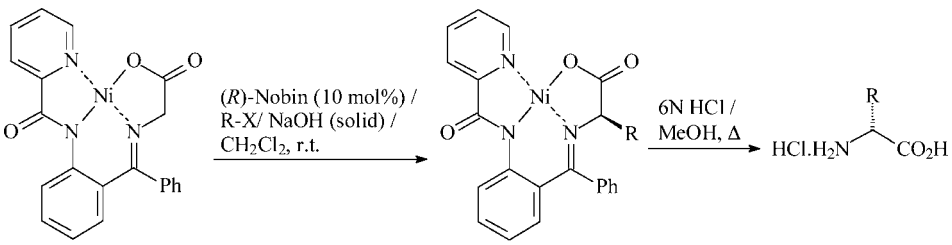
Scheme 8.12 Alkylation of substrate **16b** using Nobin as a phase-transfer catalyst.

Under solid–liquid phase-transfer conditions, amino acids **17** and **25a**,**b** were obtained from reactions using benzyl bromide, allyl bromide and 1-chloromethylnaphthalene, respectively, as the alkylating agents in the presence of 10 mol % of (*S*)-Nobin. Products **17** and **25a** were obtained with >90% yield and 67–68% *ee*, whilst product **25b** was obtained in only 60% yield and with only 18% *ee*, presumably due to the lower reactivity of the benzylic chloride-based alkylating agent.

Belokon' and Kagan screened a range of Nobin analogues, and the results obtained were consistent with the need to form an intramolecularly hydrogen bonded Nobin–sodium complex of structure **26**. Thus, Binol was catalytically inactive, presumably because both phenols can be deprotonated under the reaction conditions. *N*-methyl-Nobin was found to be about half as enantioselective as Nobin itself, but the introduction of larger groups onto the nitrogen atom or the introduction of two methyl groups almost totally destroyed the enantioselectivity, consistent with the need for an intramolecular hydrogen bond to hold the nitrogen and oxygen atoms in the correct orientation to coordinate to the sodium ion. On this basis, a mechanism exactly analogous to that shown for Taddol in Scheme 8.9 was proposed to account for the asymmetric phase-transfer ability of Nobin.

A major breakthrough in the use of Nobin as an asymmetric phase-transfer catalyst came when Belokon' and coworkers applied it to the alkylation of glycine-derived nickel(II) complex **11a** under the conditions shown in Scheme 8.13 [25]. Representative results are given in Table 8.1, which illustrate that benzylic and allylic halides react very rapidly and highly enantioselectively to produce α-amino acids. Intriguingly, in this case (*R*)-Nobin catalyzes the formation of (*R*)-amino acids, which is the opposite enantioselectivity to that observed for the alkylation of alanine derivative **16b** [21,24].

A mechanistic investigation of the Nobin-catalyzed alkylation of substrate **11a** revealed that the reaction displays an extremely large positive non-linear effect [25]. This is caused by the two enantiomers of Nobin forming a very stable – but catalytically inactive – heterochiral dimer, thus removing the minor enantiomer of Nobin from the catalytic cycle and leaving the major enantiomer of Nobin to form a complex with the sodium ion and the enolate of substrate **11a**. From a practical perspective, the non-linear effect means that amino acids with essentially identical enantiomeric excesses are obtained whether the Nobin catalyst is enantiomerically pure or has an enantiomeric excess of just 30%. Since Nobin is prepared as a racemate [26,27] and must be resolved [27,28] prior to use, this is a major synthetic



11a

Scheme 8.13 Alkylation of substrate **11a** using (*R*)-Nobin as a phase-transfer catalyst.

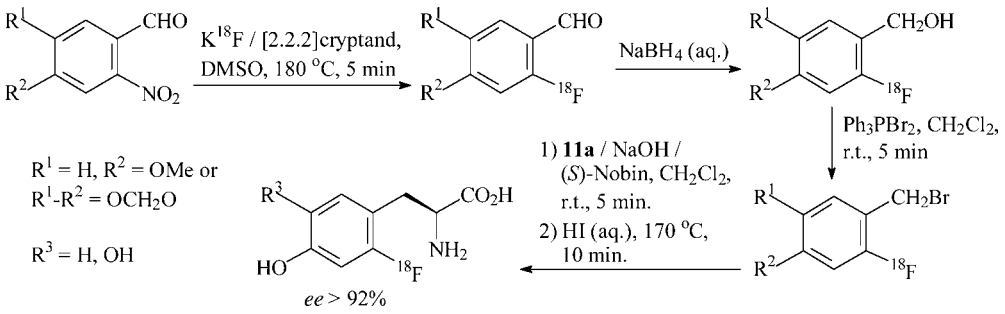
Table 8.1 Alkylation of substrate **11a** using (*R*)-Nobin as a phase-transfer catalyst.

Alkylating agent	Time (min)	Yield (%)	*ee* (%)
BnBr	8	90	97
4-$O_2NC_6H_4CH_2Br$	4	92	93
3,4-$(OCH_2O)C_6H_3CH_2Br$	6	70	98.5
3-$FC_6H_4CH_2Br$	7	80	94
2-NaphthylCH_2Br	6	62	98.5
Allyl-Br	30	68	90
Allyl-I	4	75	90
Et-I	240	35	81
n-C_6H_{13}-I	60	10	91

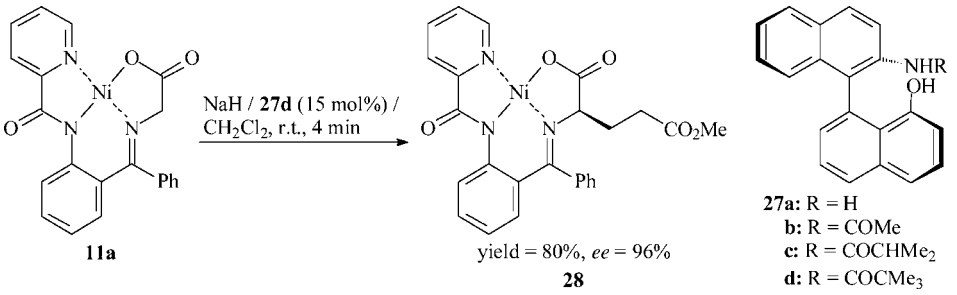
advantage. The introduction of substituents onto the nitrogen atom of the Nobin was again found to be detrimental to the catalytic activity, as was the use of solid potassium or cesium hydroxide, or aqueous sodium hydroxide as the base.

The very short reaction times required for the alkylation of substrate **11a** with benzylic bromides using Nobin as an asymmetric phase-transfer catalyst are important for the synthesis of ^{18}F-fluorinated amino acids for use in positron-emission tomography (PET)-imaging studies. Thus, Krasikova and Belokon' have developed a synthesis of 2-[^{18}F]fluoro-L-tyrosine and 6-[^{18}F]fluoro-L-Dopa employing a (*S*)-Nobin-catalyzed asymmetric alkylation of glycine derivative **11a** as the key step, as shown in Scheme 8.14 [29]. The entire synthesis (including semi-preparative HPLC purification) could be completed in 110 to 120 min, which corresponds to one half-life of ^{18}F. Both the chemical and enantiomeric purity of the final amino acids were found to be suitable for clinical use.

The use of Nobin as a catalyst for the Michael addition of the enolate of substrate **11a** to methyl acrylate was also investigated, but only relatively low levels of asymmetric induction (up to 45%) were observed [30]. In contrast, *iso*-Nobin derivatives **27a–d** were found to give much better results in this reaction [30,31]. For the Michael addition of methyl acrylate to substrate **11a**, the *N*-acylated *iso*-Nobin derivatives **27b–d** were found to be more enantioselective than the use of *iso*-Nobin **27a**. Under



Scheme 8.14 Synthesis of ^{18}F-labeled amino acids using Nobin as a phase-transfer catalyst.



Scheme 8.15 Use of *iso*-Nobin derivatives in asymmetric Michael additions.

optimal conditions (15 mol % *iso*-Nobin derivative **27d**, NaH base), Michael adduct **28** could be obtained in 80% yield and with 96% *ee* after a reaction time of just 4 min (Scheme 8.15). The short reaction time was found to be essential in this case, as longer reaction times gave a product with a lower enantiomeric excess due to racemization of compound **28** under the reaction conditions.

The use of *iso*-Nobin derivatives **27** as asymmetric phase-transfer catalysts for the alkylation of substrate **11a** was also investigated [30]. The *N*-acylated derivatives **27c** and **27d** were again found to be the most enantioselective catalysts and, under identical conditions to those employed for Nobin (see Scheme 8.13), were only slightly less enantioselective than Nobin **24**. Thus, catalyst **27d** generated phenylalanine in 70% yield and with 92% ee, compared to a 90% yield with 97% *ee* obtained with Nobin **24**, both after an 8- to 9-min reaction time in DCM. However, whereas when Nobin was used as the catalyst, the (*R*)-enantiomer of the catalyst generated (*R*)-amino acids, the use of the (*S*)-enantiomers of catalysts **27b–d** gave (*R*)-amino acids.

8.5
Use of Metal(salen) Complexes as Chiral Phase-Transfer Catalysts

On the basis of the results obtained with Taddol and Nobin, it is apparent that a chiral ligand with two heteroatoms appropriately located and held in place by an intramolecular hydrogen bond can function as an asymmetric phase-transfer catalyst. An alternative method for holding the heteroatoms in a fixed location would be the formation of a suitable metal complex involving the heteroatoms. Square planar metal(salen) complexes are known [32] to be able to use their oxygen atoms to coordinate to a second metal ion (Figure 8.1). Therefore, in 1999 Belokon' and North began a project aimed at using metal(salen) complexes as asymmetric phase-transfer catalysts.

8.5.1
Nickel(salen) Complexes

The first metal(salen) complex investigated as an asymmetric phase-transfer catalyst was methionine-derived sulfonium salt **29**. It was anticipated that the sulfonium salt

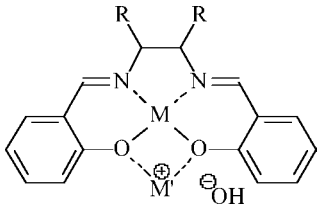
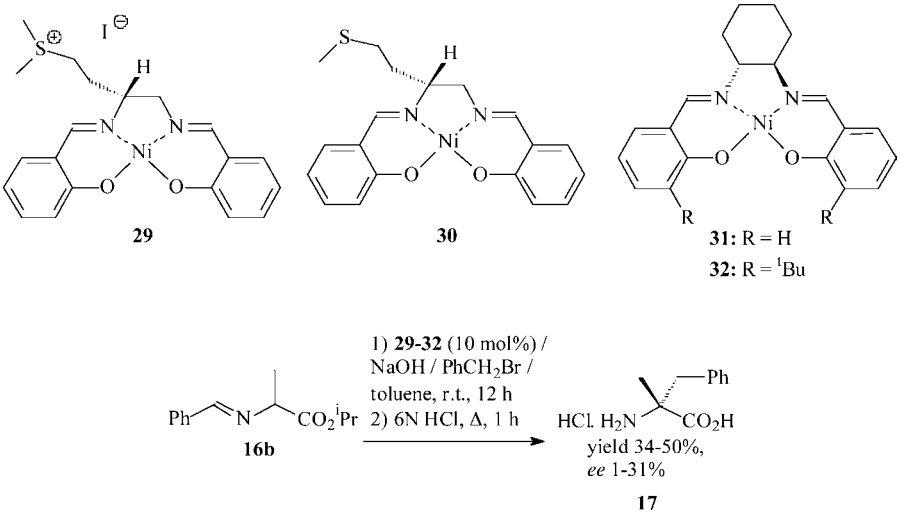


Figure 8.1 Bimetallic–salen complexes.

would function in the same way as an ammonium salt-based phase-transfer catalyst, and it was applied to the benzylation of alanine derivative **16b** under solid–liquid phase-transfer conditions (Scheme 8.16) [33]. However, complex **29** exhibited no asymmetric induction, whereas the corresponding sulfide **30** was an effective asymmetric phase-transfer catalyst (Table 8.2). This strongly suggested that the mode of action of the catalyst involved metal ion coordination by the salen oxygen atoms rather than the formation of a sulfonium hydroxide. Further evidence in favor of this mode of action was obtained by the preparation of C_2-symmetrical complexes **31** and **32**, neither of which can form a sulfonium salt. Complex **31** was found to be just as effective an asymmetric phase-transfer catalyst as complex **30**, whilst the introduction of large *tert*-butyl groups adjacent to the critical oxygen atoms (complex **32**) reduced the asymmetric induction to negligible levels. Similarly, no asymmetric induction was observed when the central nickel ion was omitted from the salen ligand, thus demonstrating the importance of the central metal ion in correctly locating the two oxygen atoms.

The low level of asymmetric induction obtained with nickel(salen) complexes was not synthetically useful, but did prove that the concept of using metal(salen) complexes as asymmetric phase-transfer catalysts was feasible. Fortunately, changing



Scheme 8.16 Use of Ni(salen) complexes in the synthesis of α-methyl phenylalanine.

Table 8.2 Use of complexes **29–32** as asymmetric phase-transfer catalysts for the benzylation of substrate **16b**.

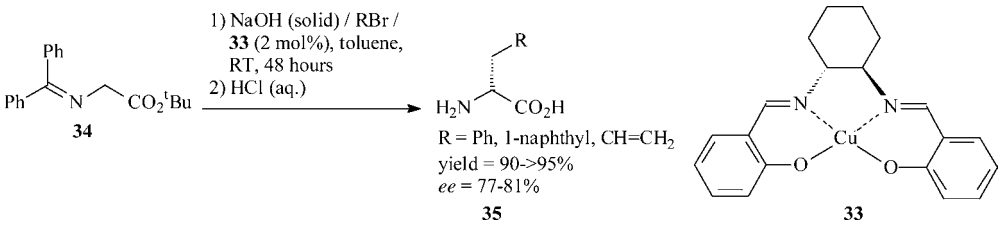
Complex	Yield (%)	*ee* (%)
29	50	1
30	44	31
31	34	30
32	47	6

the central metal ion in the salen complex resulted in much more effective asymmetric catalysts, as discussed in the following sections.

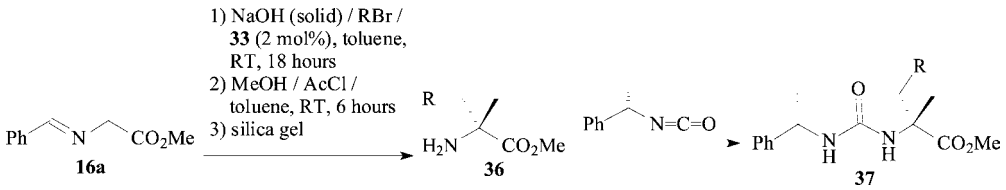
8.5.2 Copper(salen) Complexes

Catalyst screening experiments resulted in the discovery that copper(salen) complex **33** was a highly effective catalyst for the conversion of alanine derivative **16b** into (*R*)-α-methyl phenylalanine **17** under the conditions shown in Scheme 8.16. The presence of just 1 mol % of catalyst **33** was sufficient to induce the formation of compound **17** with up to 92% *ee* and in >70% yield [33]. Allyl bromide, 1-chloromethylnaphthalene and ethyl iodide also reacted with substrate **16b** to give the corresponding (*R*)-α-methyl α-amino acids in the presence of 2 mol % of complex **33** [34]. Complex **33** also catalyzed the asymmetric mono-alkylation of glycine-derived substrate **34** by benzylic or allylic halides, to give (*R*)-α-amino acid derivatives **35** with 77–81% *ee* and in greater than 90% yield, as shown in Scheme 8.17.

Esters **16b,c** are used in reactions catalyzed by cinchona alkaloid-based phase-transfer catalysts, since the size of the ester is important for efficient asymmetric induction in these reactions [35]. However, the syntheses of esters **16b,c** adds considerable cost to any attempt to exploit this chemistry on a commercial basis. Fortunately, it was possible to develop reaction conditions which allowed the readily available and inexpensive substrate **16a** to be alkylated with high enantioselectivity using catalyst **33** and sodium hydroxide, as shown in Scheme 8.18 [36]. The key feature of this modified process is the introduction of a re-esterification step following alkylation of the enolate of compound **16a**. It appears that under



Scheme 8.17 Synthesis of α-amino acids using catalyst **33**.



Scheme 8.18 Synthesis of α,α-disubstituted amino esters **36** from methyl ester substrate **16a**.

these reaction conditions, hydrolysis of the methyl ester does occur, but that this is slower than enolate formation and alkylation since, in the absence of a re-esterification step, only low yields of α,α-disubstituted amino acids could be obtained. The modified work-up conditions shown in Scheme 8.18 also allowed the isolation of amino acid methyl esters **36**, and the enantiomeric excess of these could readily be determined by ^{1}H NMR analysis of the corresponding diastereomeric ureas **37**. Under the conditions shown in Scheme 8.18, a range of benzylic, allylic and propargylic halides was found to react with substrate **16a** to give α-methyl amino esters, as detailed in (Table 8.3).

The optimal reaction conditions for reactions involving catalyst **33** and substrates **16a–c** or **34** were investigated, and it was found that best results were obtained at room temperature [36] with toluene as the solvent [37] and with sodium hydroxide or sodium hydride as the base. In particular, the use of potassium hydroxide always gave lower enantioselectivities than sodium hydroxide, and lithium hydroxide was not effective in these reactions. Attempts to use aqueous sodium hydroxide as the base under liquid–liquid phase-transfer conditions resulted in the formation of a negligible amount of product [33,34]. An important finding of these optimization studies was the presence of a significant background reaction [38]. Hence, one role of catalyst **33** must be to enhance the reactivity of an enolate when it is coordinated to the catalyst relative to the uncoordinated enolate.

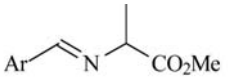
The structure of the imine substrate was also optimized. Since the use of amino acid methyl ester-derived substrates was highly desirable, the only aspect of substrate

Table 8.3 Use of complex **33** as an asymmetric phase-transfer catalysts for the alkylation of substrate **16a**.

Entry	Alkylating agent	Yield (%)	*ee* (%)
1	Benzyl-Br	91	81
2	4-$O_2NC_6H_4CH_2Br$	78	85
3	4-$MeOC_6H_4CH_2Cl$	42	60
4[a)]	4-$MeOC_6H_4CH_2Cl$	72	69
5	1-Bromomethylnaphthalene	85	86
6	2-Bromomethylnaphthalene	82	84
7	Allyl bromide	75	72
8	Cinnamyl bromide	95	77
9	Propargyl bromide	70	43

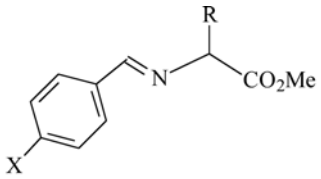
[a)] NaH used as the base.

16a which could be varied was the nature of the aromatic group within the imine. This group could exert a steric effect on the enolate alkylation, and could also affect the acidity of the α-proton, thus changing the relative rates of the catalyzed and uncatalyzed reactions. Hence, substrates **38** containing imines of different steric and electronic properties were prepared and alkylated with benzyl bromide according to the conditions shown in Scheme 8.18 [37,39] No obvious steric effect was apparent from this study and both strongly electron-withdrawing and electron-donating groups on the aryl imine were also detrimental. However, introduction of halo-substituents onto the imine was found to be beneficial to the enantioselectivity, and optimal results were obtained with 4-chlorobenzylidene derivative **38f**, which gave methyl ester **36** (R=Ph) with 92% enantiomeric excess, as opposed to 81% enantiomeric excess obtained using substrate 16a.



38a: Ar = 1-naphthyl
b: Ar = 2-naphthyl
c: Ar = 4-$MeOC_6H_4$
d: Ar = 4-$NO_2C_6H_4$
e: Ar = 4-FC_6H_4
f: Ar = 4-ClC_6H_4
g: Ar = 4-BrC_6H_4
h: Ar = 4-IC_6H_4
i: Ar = 2-ClC_6H_4
j: Ar = 3-ClC_6H_4

Whilst the use of asymmetric phase-transfer catalysts to alkylate glycine derivative **34** and alanine derivatives **16b**,**c** was well established using a variety of phase-transfer catalysts, only Maruoka's spiro-ammonium salt catalysts had been investigated for the alkylation of other amino acid derivatives [40]. Therefore, a range of substrates **39a–g** was prepared to investigate the effect of the size and nature of the amino acid side chain on the enantioselectivity of the alkylation catalyzed by complex **33**, according to Scheme 8.18. The results of this study are presented in Table 8.4. α-Aminobutyric acid has a side chain which is only slightly larger than that of alanine, and the alkylation of substrate **39a** was found to be both slower (Table 8.4, entries 1 and 2) and slightly less enantioselective (entries 1–3) than the corresponding alkylations of substrate **16a**. However, it was still possible to obtain both α-benzyl and α-allyl aminobutyric acid derivatives with 80–82% *ee* [38,41].



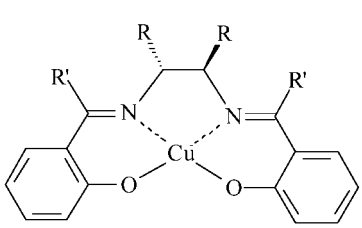
39a: R = Et; X = Cl
b: R = CH_2CHMe_2; X = Cl
c: R = CH_2Ph; X = Cl
d: R = $CHMe_2$; X = Cl
e: R = CH_2CO_2Me; X = H
f: R = $CH_2CH{=}CH_2$; X = H
g: R = Ph; X = H

Table 8.4 Influence of the side chain on the alkylation of substrates **39a–g**.

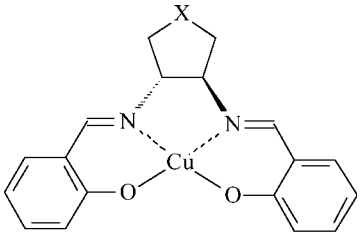
Entry	Substrate	Side chain	R-Br (equiv.)	33 (mol%)	Time (days)	Yield (%)	*ee* (%)
1	**39a**	Et	Bn-Br (1.2)	2	1	39	80
2	**39a**	Et	Bn-Br (1.2)	2	2	91	82
3	**39a**	Et	Allyl-Br (1.2)	2	1	46	80
4	**39b**	CH_2CHMe_2	Bn-Br (1.2)	10	7	54	55
5	**39b**	CH_2CHMe_2	Allyl-Br (1.2)	10	1	46	22
6	**39c**	CH_2Ph	Allyl-Br (1.2)	2	1	30	17
7	**39c**	CH_2Ph	Allyl-Br (1.2)	10	1	40	31
8	**39c**	CH_2Ph	Allyl-Br (1.2)	25	1	68	37
9	**39e**	CH_2CO_2Me	Allyl-Br (1.2)	2	1	27	17
10	**39e**	CH_2CO_2Me	Bn-Br (1.2)	2	1	75	10
11	**39f**	$CH_2CH{=}CH_2$	Bn-Br (1.2)	2	1	66	57
12	**39g**	Ph	Allyl-Br (1.2)	2	1	31	48
13	**39g**	Ph	Bn-Br (1.2)	2	1	38	42

Leucine derivative **39b** has a side chain which branches at the γ-position, and this substrate could not be alkylated under the standard reaction conditions. However, by increasing the amount of catalyst **33** to 10 mol %, the reaction did occur with both benzyl bromide and allyl bromide (Table 8.4, entries 4 and 5), although the reaction with benzyl bromide was very slow (entry 4) and in both cases the enantioselectivity was significantly lower than that obtained from substrates **16a** and **39a**. Similar results were obtained with phenylalanine-derived substrate **39c** which also branches at the γ-position (Table 8.4, entries 6–8). Both the yield and enantioselectivity increased as the amount of catalyst **33** used increased, although even when 25 mol % of catalyst was employed only a moderate enantioselectivity was obtained (entry 8). No conditions could be found under which valine derivative **39d** would undergo any reaction with allyl or benzyl bromide. This substrate has a branch at the β-carbon, and so is significantly more sterically hindered than substrates **39a–c**. Aspartic acid derivative **39e** also has a side chain which branches at the γ-position, but this time with added functionality present. This substrate could only be alkylated with low enantioselectivity (Table 8.4, entries 9 and 10), and when allyl bromide was used as the alkylating agent, the yield and enantioselectivity were essentially identical to those observed using substrate **39c** (entries 6 and 9). Allyl glycine derivative **39f** has an unbranched side chain, and so was expected to be alkylated with high enantioselectivity. In the event (entry 11), it reacted with benzyl bromide under the standard reaction conditions to give a product in good yield but with only moderate enantioselectivity. This lower enantioselectivity may however be partly due to the non-optimal imine present in substrate **39f**. The reactions of substrate **39c** with allyl bromide (Table 8.4, entries 6–8) and of substrate **39f** with benzyl bromide (entry 11) gave opposite enantiomers of the same product, consistent with a common origin for the asymmetric induction in both cases. Finally, phenylglycine derivative **39g**, which has

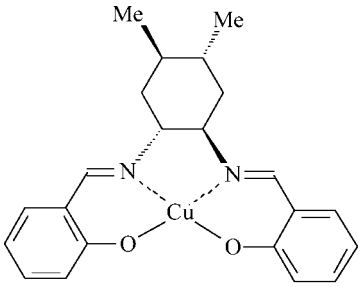
a side chain branched at the β-position, was alkylated with moderate enantioselectivity under the standard reaction conditions (entries 12 and 13). This was a surprisingly good result compared to the use of substrate **39d**, and may be due to the formation of a planar enolate from substrate **39g**, as discussed below.



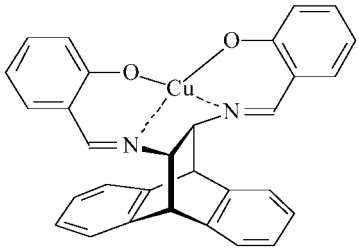
40a : R = Me; R' = H
b : R = Ph; R' = H
c : R = Ph; R' = Ph
d : R = ^{t}Bu; R' = H



41a: X = CH_2
b: X = NBn

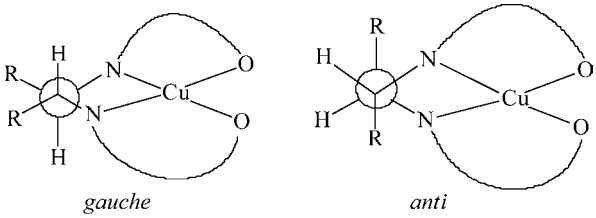


41c



41d

Belokon' and North have made comprehensive efforts to optimize the structure of copper catalyst **33**. Complexes **40a–d** (derived from acyclic diamines) and **41a–d** (derived from cyclic diamines) were prepared and tested as catalysts for the alkylation of substrate **16a**, as shown in Scheme 8.18, using benzyl bromide as the alkylating agent [42]. All of these complexes were significantly less enantioselective (giving product **36** (R=Ph) with 0 to 37% *ee*). However, a correlation between the conformation of the complex and its enantioselectivity was noted. Thus, complexes **40a–d** can adopt a conformation in which the R-groups are either *anti*- or *gauche*-to one another (Figure 8.2). The *anti*-conformation is usually energetically preferred as this



gauche *anti*

Figure 8.2 *Gauche*- and *anti*-conformations of a copper(salen) complex.

minimizes steric interactions between the two R-groups. In the case of complexes **40a–d**, the percentage occupancy of the diaxial conformation would be expected to increase in the order **40a** < **40b** < **40c** < **40d**, and the enantioselectivity of the catalysts was found to decrease in the same order. Complex **40d** was completely inactive, and the X-ray structure of this complex [42] revealed that the *tert*-butyl groups are both in *anti*-positions and extend over and below the copper ion, thus preventing any interaction between the copper ion and the enolate of substrate **16a**. Complexes **41a–d** derived from cyclic diamines are constrained to a *gauche*-conformation, and these all gave similar (25–32%) enantioselectivities. Thus, the results obtained with complexes **40a–d** and **41a–d** suggest that the catalysts are active in a conformation in which the substituents on the diamine are *gauche*-to one another.

All of complexes **41a–d** were significantly less enantioselective than complex **33**. In the case of complexes **41a**,**b**, this may be due to conformational flexibility within the five-membered ring. For complex **41c**, both methyl groups are forced to adopt axial positions on the cyclohexane ring, and this may suggest that the unfavorable influence of axially located substituents extends beyond the ethylene diamine unit. Finally, in complex **41d** the cyclohexane ring is in a boat rather than a chair conformation, and this or the phenyl substituents may account for the low level of asymmetric induction observed.

One of the main advantages associated with the use of salen complexes as asymmetric catalysts is the ease with which the steric and electronic properties of the chiral complex can be optimized by the introduction of substituents onto the aromatic rings of the salen ligand. In most cases, large substituents on the aromatic rings were found to significantly enhance the enantioselectivity of the catalyst. However, Belokon' and North have prepared a large number of analogues of complex **33** with substituents at every position of the aromatic rings [34,37,39]. The substituents were chosen to exert a steric (e.g., *tert*-butyl group), electronic (e.g., OMe or NO_2 group) or sodium ion-complexing [43] (e.g., hydroxy, polyether, crown-ether) effect. Whilst complexes possessing only remote alkyl substituents displayed enantioselectivities of between 7 and 80%, none of these catalysts was any improvement on complex **33**. The introduction of substituents adjacent to the oxygen atoms of the salen ligand significantly reduced the catalytic activity of the complexes, as previously observed for nickel(salen) complex **32**. One reason for this failure to enhance catalytic activity may be related to the solubility of the complexes. Complex **33** is insoluble in toluene, but in the presence of solid sodium hydroxide a deep red-colored solution is formed, indicating that the complex **33**/sodium complex is soluble in the reaction solvent. For some of the substituted catalysts, the complex formed with sodium hydroxide may not be soluble in toluene, thus accounting for the lack of catalytic activity.

The alkylation of substrates **16** or **34** by catalyst **33** was found to exhibit a pronounced positive non-linear effect [34]. In addition, there was an optimal concentration of catalyst **33** in these reactions, with higher or lower catalyst concentrations being detrimental to the asymmetric induction [41]. These results are consistent with a dimeric form of catalyst **33** being catalytically active and in equilibrium with catalytically inactive monomeric and oligomeric species. On the basis of these results,

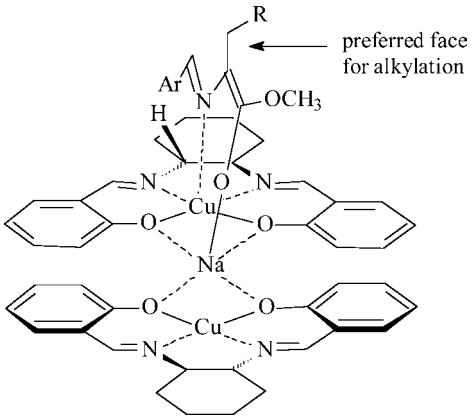


Figure 8.3 A model to explain the asymmetric induction obtained using catalyst **33**.

the model shown in Figure 8.3 has been developed to explain the asymmetric induction [38,41].

In this model, the enolate is chelated to both the sodium and copper ions, with the harder oxygen atom binding to the sodium, whilst the softer nitrogen atom of the enolate coordinates to the copper ion. This holds the enolate in a plane which is orthogonal to the plane of the copper(salen) complexes, with reaction on the *re*-face of the coordinated enolate being less hindered than reaction on the *si*-face due to the influence of the highlighted axial hydrogen atom. However, if the catalyst contains any larger group in axial positions (as in complexes **40a–d**), these disrupt the coordination of the enolate and hence destroy the catalytic activity of the complex. Substituents adjacent to the oxygen atoms of the salen ligand will inhibit formation of the dimeric sodium complex, thus destroying the catalytic activity. If the substituent is located at any other position, it will have a similar influence on both faces of the coordinated enolate, but will tend to reduce the difference between the two faces of the enolate and hinder attack at either face, thus reducing both the enantioselectivity and reactivity of the catalyst. This model can readily be incorporated (as the equivalent of structure **19**) into the standard mechanism (Scheme 8.9) for asymmetric phase-transfer catalyzed enolate alkylation as previously developed for Taddol- and Nobin-catalyzed reactions, thus giving a single unified mechanism for all of these reactions.

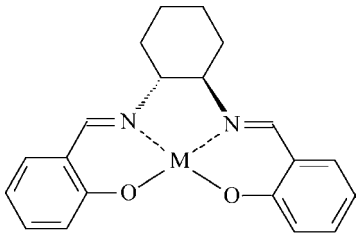
For substrates derived from amino acids other than glycine or alanine, the side chain of the amino acid also needs to be considered. Rotation around the C_α–C_β bond of the enolate could locate the side chain over the *re*-face (as shown in Figure 8.3) or over the *si*-face. It is likely that the side chain will prefer to be on the sterically less-hindered *re*-face of the enolate, so it will hinder the approach of the electrophile to this face and this will result in a lower enantioselectivity during the alkylation. The overall rate of reaction will also decrease as the size of the side chain increases. Thus, the model shown in Figure 8.3 correctly predicts both the absolute configuration of the product and the dependence of the enantioselectivity on the size of the amino acid side chain. Substrate **39g** derived from phenylglycine provides a way to probe the

stereochemical model shown in Figure 8.3. The enolate of substrate **39g** should be completely planar, so the side chain should not hinder either face of the enolate. The asymmetric induction observed with substrate **39g** (Table 8.4) was 40–50%, which is significantly higher than that obtained using any other substrate with a branched side chain under the same reaction conditions, consistent with the model shown in Figure 8.3.

One unusual feature of alkylation reactions using catalyst **33** is that only benzylic, allylic and propargylic halides are suitable alkylating agents [36]. Simple alkyl halides (such as methyl iodide) are totally unreactive under the reaction conditions. To investigate this effect, a Hammett analysis in which substrate **16a** was allowed to react with an excess of benzyl bromide and a substituted benzylic bromide was carried out [44]. This investigation revealed that the enolate of substrate **16a** reacted selectively with the more electron-deficient of the two benzylic halides, and that this effect occurred in both catalyzed and uncatalyzed reactions, but was more pronounced in the former. Thus, it appears that coordination of the enolate to complex **33** increases the nucleophilicity of the enolate, leading to a more asynchronous S_N2-type reaction in which formation of the new carbon–carbon bond is faster than cleavage of the carbon–bromine bond. This is consistent with coordination of the enolate to the catalyst increasing its reactivity as required to overcome the background reaction noted for these alkylations. Although at present the origin of the increased nucleophilicity is unclear, it may be related to electron donation from the copper ion into the enolate, or to the coordinated enolate being slightly twisted resulting in reduced delocalization of the negative charge over the ester and imine groups.

8.5.3
Use of Other Metal(salen) Complexes as Catalysts for Enolate Alkylation

Since both nickel(II) and copper(II)(salen) complexes have been found to form asymmetric phase-transfer catalysts, the use of other metal(salen) complexes was investigated. Cobalt(salen) complexes **42a–d** provided an opportunity to probe the influence of the oxidation state of the metal on the catalytic activity of the complex [42]. Hence, each of these complexes was prepared and tested as a catalyst for the benzylation of substrate **16a**, according to the conditions specified in Scheme 8.18.



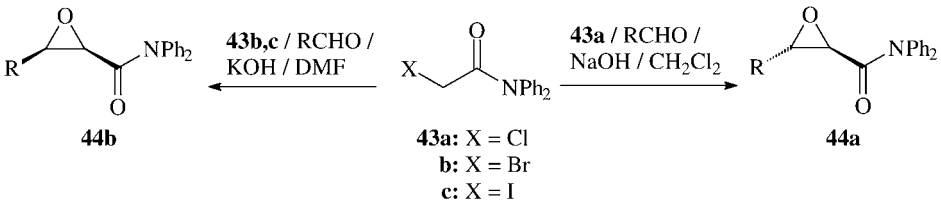
42a: M = Co
b: M = Co-I
c: M = Co^+ PF_6^-
d: M = Co-Na

The X-ray structure of complex **42a** [42] showed it to be square planar, and essentially superimposable on the X-ray structure of Cu(salen) complex **33** [45]. Complex **42a** was found to be catalytically active, and gave (*R*)-α-methyl-phenylalanine methyl ester in 83% yield and with 80% *ee* – results which are essentially identical to those obtained using complex **33**. Changing the substrate to compound **38f** [which was optimal for the use of copper(salen) complex **33**] further increased the enantioselectivity of the reaction to 85%. Experimentally, complex **42a** has an advantage compared to copper(salen) complex **33** as it does not require chromatographic purification on Sephadex-LH20 to obtain a pure catalyst.

In contrast, the cobalt(III) and cobalt(I) complexes **42b–d** were found to be catalytically inactive, thus emphasizing the importance of a metal in the +2 oxidation state for the formation of an active catalyst. Iron(II), manganese(II) and zinc(II) salen complexes were also screened as catalysts, and found to be inactive. Such inactivity is most likely due to the complexes being octahedral rather than square planar. Rhodium(II), palladium(II) and platinum(II) complexes were also inactive, probably due to the larger transition metals locating the salen oxygen atoms too far away from one another to form a sodium chelate, as required by the model in Figure 8.3. In another study [46], a range of metal(salen) complexes derived from transition metals, main-group metals and lanthanides were screened for their ability to catalyze the reaction between substrate **16b** and benzyl bromide, and similar conclusions were drawn as to the requirements for catalytic activity.

8.5.4
Metal(salen) Complexes as Catalysts for Darzens Condensations

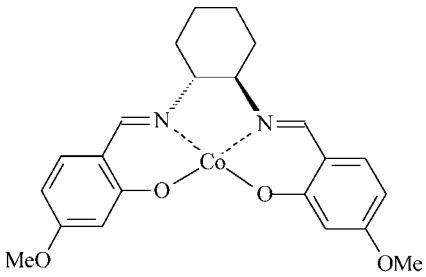
Very recently, Belokon' and North have extended the use of square planar metal–salen complexes as asymmetric phase-transfer catalysts to the Darzens condensation. These authors first studied the uncatalyzed addition of amides **43a–c** to aldehydes under heterogeneous (solid base in organic solvent) reaction conditions, as shown in Scheme 8.19 [47]. It was found that the relative configuration of the epoxyamides **44a**,**b** could be controlled by choice of the appropriate leaving group within substrate **43a–c**, base and solvent. Thus, the use of chloro-amide **43a** with sodium hydroxide in DCM gave predominantly or exclusively the *trans*-epoxide **44a**; this was consistent with the reaction proceeding via a thermodynamically controlled aldol condensation



Scheme 8.19 Diastereocontrolled Darzens condensations under heterogeneous reaction conditions.

involving a chelated transition state. In contrast, the use of substrates **43b**,**c** which contain a better leaving group with potassium hydroxide in dimethylformamide (DMF), gave predominantly or exclusively *cis*-epoxide **44b**, which is the expected product from a kinetically controlled aldol condensation involving an open-chain transition state.

Having found heterogeneous reaction conditions under which the diastereoselectivity of the Darzens condensation could be controlled, Belokon' and North proceeded to investigate the use of asymmetric phase-transfer catalysts to control the absolute configuration of the products [48]. A wide range of metal(salen) complexes were screened, with both the metal and structure of the salen ligand being varied. Only cobalt(II)(salen) complexes were found to induce significant enantioselectivity, and the best catalyst discovered in this preliminary study was complex **45**. The optimal conditions for reactions catalyzed by complex **45** involved the use of 2 mol % of the catalyst with DCM as solvent and either substrate **43a** with rubidium hydroxide as the base to give predominantly *trans*-epoxide **44a**, or substrate **43b** with potassium hydroxide as the base to give mainly *cis*-epoxide **44b**. Under these conditions, *trans*-epoxides **44a** could be formed with up to 43% *ee* (in favor of the 2*S*,3*R*-enantiomer), whilst *cis*-epoxides **44b** could be formed with up to 50% *ee* in favor of the 2*S*,3*S*-enantiomer. At this stage, the origin of the asymmetric induction induced by complex **45** is not clear, but there is clearly scope to study the mechanistic aspects of the reaction and to use the resulting information to further enhance the enantioselectivity of the reaction.



45

8.6 Conclusions

Although, historically, asymmetric phase-transfer catalysis has been carried out using chiral ammonium salts as the phase-transfer agents, over the past 10 years it has been shown that a variety of metal-complexing agents or preformed metal (ligand) complexes can also form highly effective phase-transfer catalysts. The formation of an effective asymmetric phase-transfer catalyst of this type requires, however, that the metal-chelating groups are held rigidly in appropriate locations.

This can be achieved by cyclization (crown ethers), by the formation of an intramolecular hydrogen bond (Taddol and Nobin), or by use of a second metal ion to correctly position the chelating atoms within its coordination sphere (metal (salen) complexes).

Currently, this area is not as well developed as the use of cinchona alkaloid derivatives or spiro-ammonium salts as asymmetric phase-transfer catalysts, and the key requirements for an effective catalyst are only just becoming apparent. As a result, the enantioselectivities observed using these catalysts rarely compete with those obtainable by ammonium ion-derived phase-transfer catalysts. Nevertheless, the ease with which large numbers of analogues – of Taddol, Nobin, and salen in particular – can be prepared, and the almost infinite variety for the preparation of new, chiral metal(ligand) complexes, bodes well for the future development of more enantioselective versions of these catalysts.

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9
Chiral Quaternary Ammonium Fluorides for Asymmetric Synthesis

Seiji Shirakawa, Takashi Ooi, and Keiji Maruoka

9.1
Introduction

Quaternary ammonium fluorides, particularly tetraalkylammonium fluorides, have been widely recognized as a convenient, organic-soluble source of naked fluoride ion. Their utility in modern organic synthesis has been well documented on numerous occasions, taking advantage of either the nucleophilic affinity of fluoride ion to a silicon atom or its eminent basicity in aprotic solvents [1,2]. The former property enables the fluoride-mediated generation of nucleophiles from organosilicon compounds, while the latter property allows the direct generation of nucleophiles through a deprotonation process. Both processes have been utilized for the subsequent selective bond-forming reactions under mild conditions. These synthetically useful metal-free methods have implications for the development of asymmetric versions based on the use of chiral, non-racemic quaternary ammonium fluorides, providing a unique platform for establishing otherwise difficult asymmetric transformations. In this chapter, some research investigations devoted to the development of structurally well-defined chiral ammonium fluorides are outlined, together with details of their utilization for various stereoselective carbon–carbon bond-formation reactions. Taken together, these provide a basis for future studies in the field of enantioselective organocatalysis.

9.2
In-Situ Generation of Chiral Quaternary Ammonium Fluorides

In 1978, Wynberg and coworkers reported the first example of a chiral quaternary ammonium fluoride-catalyzed Michael addition of nitromethane to chalcone (Scheme 9.1) [3]. The reaction was performed in toluene at 20 °C with 10 mol% of chiral ammonium salt **1** or **3a** and excess potassium fluoride (KF, 15 equiv.), yielding the γ-nitro ketone with 10–23% enantiomeric excess (ee). The requisite chiral

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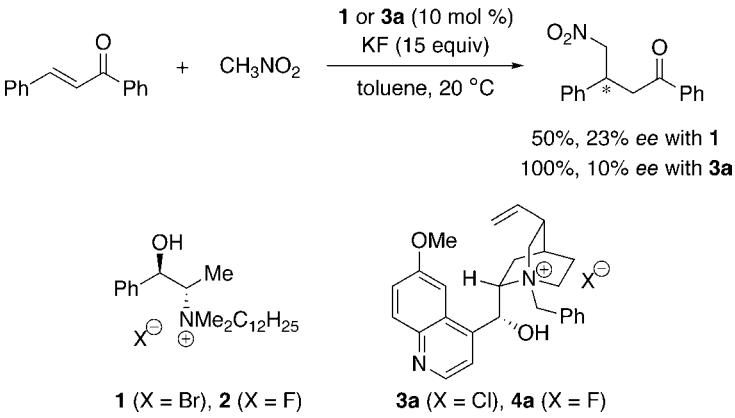
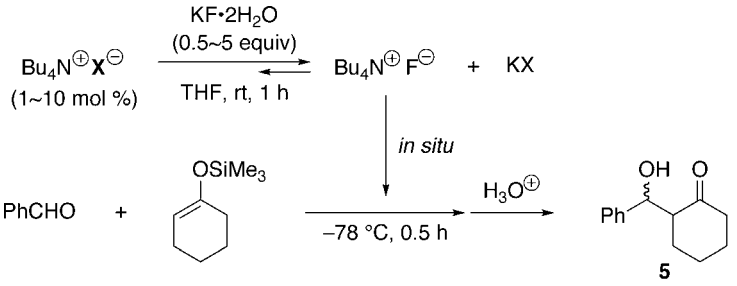


Scheme 9.1

ammonium fluorides **2** and **4a** were generated *in situ* from the corresponding bromide and chloride through anion exchange with KF.

A study conducted by Carpino and Sau showed that a mixture of tetrabutylammonium chloride and potassium fluoride dihydrate ($KF{\cdot}2H_2O$) in acetonitrile can be used as a convenient source of fluoride ion [4]. Such *in-situ* generation techniques have obvious synthetic merit because they obviate the preparation and purification of highly hygroscopic anhydrous ammonium fluorides. This is quite advantageous for the design and preparation of effective chiral quaternary ammonium fluorides. In this regard, the aim was to develop a more efficient combination by focusing on the effect of the counterion of the parent ammonium salts [5]. Since the catalytic activity of tetrabutylammonium fluoride (TBAF) in fluoride ion-catalyzed reactions has been well documented [6], various tetrabutylammonium salts (TBAX) were employed as a precursor, after which anion exchange with excess $KF{\cdot}2H_2O$ in tetrahydrofuran (THF) was examined. The effectiveness of this procedure was evaluated by subsequently performing aldol reactions of 1-trimethylsiloxycyclohexene with benzaldehyde in a one-pot reaction under identical conditions. As shown in Scheme 9.2, the efficiency was indeed profoundly influenced by the anion (X). Although the expected anion exchange was certainly achieved with tetrabutylammonium chloride (TBAC) to catalyze the cross-aldol reaction, the reactivity was far less than that of TBAF itself. Interestingly, comparable catalytic activity was attained by the use of $TBAHSO_4$ as a precursor, leading to formation of the desired β-hydroxy ketone **5** in 91% isolated yield; eventually, it was found that 0.5 equiv. of $KF{\cdot}2H_2O$ was sufficient for a smooth reaction. This system was especially advantageous when the reaction was conducted with a reduced amount of $TBAHSO_4$ (1 mol%), where the catalytic activity of the *in situ*-generated TBAF was found to be markedly enhanced compared to that with 1 mol% of TBAF itself.

The usefulness of the present system was then demonstrated by its application to the *in-situ* generation of structurally rigid, C_2-symmetric chiral quaternary ammonium fluorides of type **6** (X = F) from the corresponding hydrogen sulfate **6** ($X = HSO_4$), and their direct use for the asymmetric aldol reactions (Scheme 9.3). For instance,



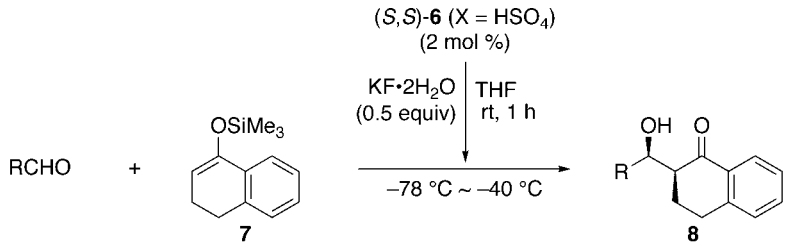
X = I, Br, IO_4, ClO_4, BPh_4, OTf : no reaction
X = Cl (10 mol %), KF•$2H_2O$ (5 equiv) : 5% (*erythro*/*threo* = 43:57)
F (10 mol %) : 89% (40:60)
HSO_4 (10 mol %), KF•$2H_2O$ (5 equiv) : 91% (25:75)
HSO_4 (10 mol %), KF•$2H_2O$ (0.5 equiv) : 91% (23:77)
HSO_4 (1 mol %), KF•$2H_2O$ (0.5 equiv) : 86% (32:68) } *At –40 °C*
F (1 mol %) : 24% (58:42) } *for additional 2h*

Scheme 9.2

mixing (*S*,*S*)-**6a** (X = HSO_4, 2 mol%) and KF·$2H_2O$ (0.5 equiv.) in THF at room temperature for 1 h and subsequent treatment with benzaldehyde and enol trimethylsilyl ether **7** at −78 °C for 30 min gave rise to the desired α-hydroxy ketone **8** (R = Ph) in 84% yield (*erythro*/*threo* = 57 : 43) with 31% *ee* for the major *erythro* isomer. Further, employment of (*S*,*S*)-**6b** (X = HSO_4) having a 3,5-bis-(trifluoromethyl)phenyl group as catalyst precursor resulted in the formation of **8** (R = Ph) in 92% yield (*erythro*/*threo* = 70 : 30) with 76% *ee* (*erythro* isomer). This beneficial effect of the electron-withdrawing trifluoromethyl group could be understood by tight contact ion pairing of the ammonium enolate due to the decrease of electron density on the nitrogen atom of the catalyst [7]. In addition, the crucial role of toluene as a co-solvent for improvement of the stereoselectivities was uncovered, and the reaction with α-naphthaldehyde under similar conditions exhibited excellent diastereo- and enantioselectivities [5].

The efficient *in-situ* generation of chiral quaternary ammonium fluorides from the corresponding hydrogen sulfates has also been successfully applied to the aldol reaction of ketene silyl acetal **9** with aldehydes for the synthesis of biologically important β-hydroxy-α-amino acid esters (Table 9.1) [8]. A mixture of chiral ammonium hydrogen sulfate (*S*,*S*)-**6c** (2 mol%) and potassium fluoride (KF, 1 equiv.) in THF was well stirred at room temperature for 1 h. Aldehyde (2 equiv.) and a toluene solution of ketene silyl acetal **9** were then added at −78 °C, and stirring continued at −78 °C∼−40 °C for several hours. Subsequent acidic hydrolysis with 1 M HCl afforded the corresponding *anti*-β-hydroxy-α-amino ester **10**, predominantly with excellent enantioselectivity.

Further application of the *in-situ* generation of chiral quaternary ammonium fluorides from the corresponding hydrogen sulfates has also been shown in the facile preparation of optically active esters *via* the alkylative kinetic resolution of secondary alkyl halides. For example, simple stirring of the mixture of 3-phenylpropionic acid, 1-(1-bromoethyl)naphthalene, (*S*,*S*)-**6b** (X = HSO_4; 2 mol%) and KF·$2H_2O$ (5 equiv.)

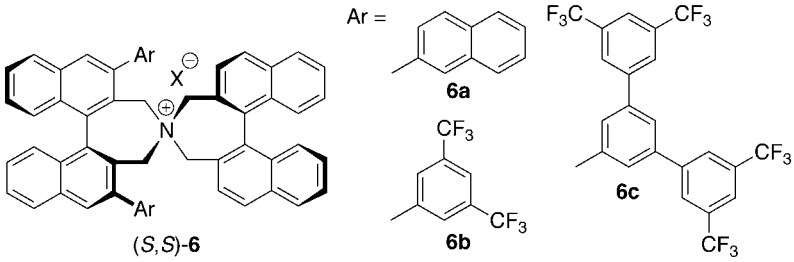


THF solvent at –78 °C

R = Ph (*S*,*S*)-**6a** : 84% (*erythro*/*threo* = 57:43), 31% ee (*erythro* isomer) (*S*,*S*)
(*S*,*S*)-**6b** : 92% (70:30), 76% *ee* (*S*,*S*)

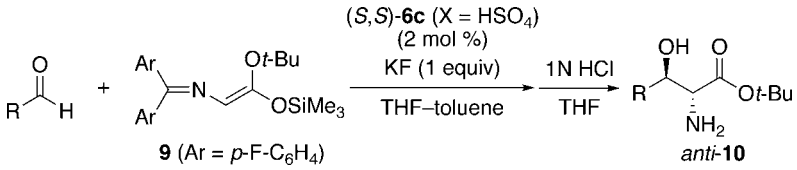
THF–toluene (2:1) at –78 °C ~ –40 °C

R = Ph (*S*,*S*)-**6b** : 90% (83:17), 84% *ee* (*S*,*S*)
R = α-Np (*S*,*S*)-**6b** : 90% (94:6), 91% *ee* (*S*,*S*)

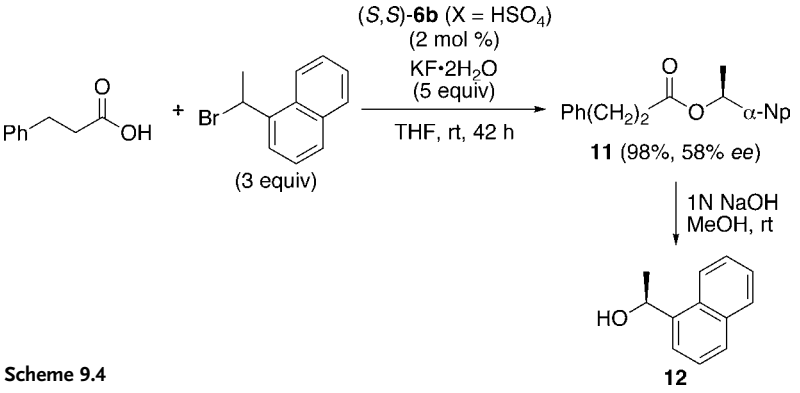


Scheme 9.3

Table 9.1 Asymmetric Mukaiyama-type aldol reactions of a glycine derivative catalyzed by *in situ*-generated chiral quaternary ammonium fluoride.



Entry	R	Conditions (°C, h)	Yield (%) (*anti*/*syn*)	*ee* (%) (*anti*)
1	$Ph(CH_2)_2$	−78, 12; −40, 3	77 (8.3:1)	92
2	$CH_3(CH_2)_4$	−78, 12; −40, 3	58 (8.4:1)	91
3	$CH_3(CH_2)_5$	−78, 12; −40, 2	72 (11:1)	90
4	*i*-Bu	−78, 16; −40, 3	70 (7.2:1)	90
5	*i*-Pr	−78, 11; −40, 1	65 (6.7:1)	97

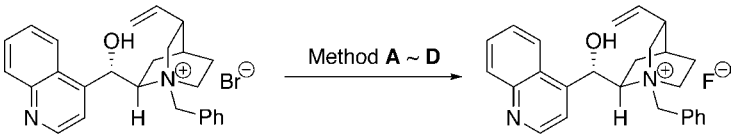


Scheme 9.4

in THF at room temperature for 42 h gave rise to the desired ester **11** in 98% isolated yield with 58% ee, from which enantioenriched secondary alcohol **12** was readily obtained by basic hydrolysis (Scheme 9.4) [9].

9.3 Chiral Quaternary Ammonium Fluorides: Preparation and Application to Organocatalytic Asymmetric Reactions

Shioiri and coworkers systematically investigated the preparation of *N*-benzylcinchonium fluoride **4b** from the corresponding bromide **3b** (Scheme 9.5) [10]. In methods A and B, the anion-exchange resins of F^- form were used [11], while neutralization of the ammonium hydroxide was involved in method C [12]. In method D, silver fluoride (AgF) was employed for the direct anion exchange [13]. The fluoride **4b** thus obtained was dried over P_2O_5 at 40 °C under vacuum overnight. Subsequent ^1H NMR analysis of **4b** indicated no decomposition of the *N*-benzylcinchonium residue, while ^{19}F NMR measurements in CD_2Cl_2 showed a peak centered at ca. −124 ppm ($CFCl_3$ as an internal standard) [14]. Both, the catalytic activity and chiral efficiency of **4b** were then evaluated in the asymmetric aldol reaction of enol silyl ether of 2-methyl-1-

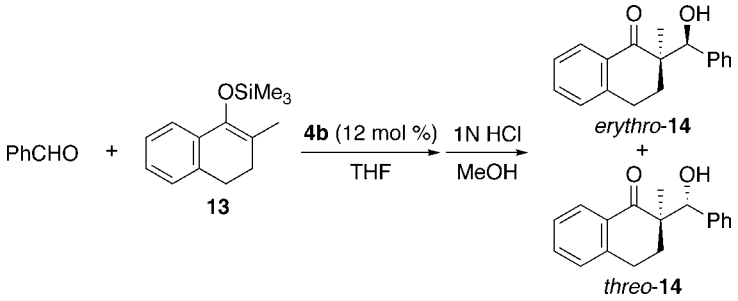


3b **4b**

Method **A** : 1) Amberlite IRA-410 F^- form, 2) Evaporation
Method **B** : 1) Amberlite A-26 F^- form, 2) Evaporation
Method **C** : 1) AmberliteA-26 OH^- form, 2) 1N HF, 3) Evaporation
Method **D** : 1) AgF, 2) Filtration, 3) Evaporation

Scheme 9.5

Table 9.2 Asymmetric Mukaiyama aldol reactions catalyzed by chiral quaternary ammonium fluorides **4b** with various methods of preparation.



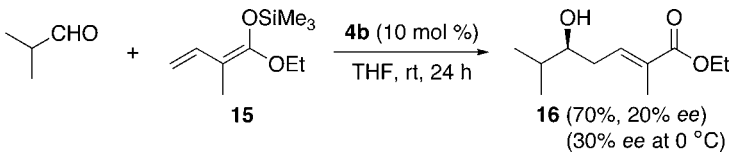
Entry	Method	Yield (%)	*erythro/threo*	*ee* (%) (*erythro/threo*)
1	**A**	74	75:25	72/22
2	**B**	63	71:29	67/13
3	**C**	74	70:30	70/20
4	**D**	66	80:20	71/16

tetralone (**13**) with benzaldehyde (Table 9.2) [10]. The chemical yields and diastereo- and enantioselectivities of **14** were found to be substantially independent of the preparation method of **4b**.

Further examination of the fluoride ion-catalyzed asymmetric aldol reaction of the enol silyl ethers prepared from acetophenones and pinacolone with benzaldehyde using **4b** and its pseudoenantiomer **4c** revealed the dependence of the stereochemistry of the reactions on the hydroxymethyl-quinuclidine fragment of the catalyst (Table 9.3) [10,15].

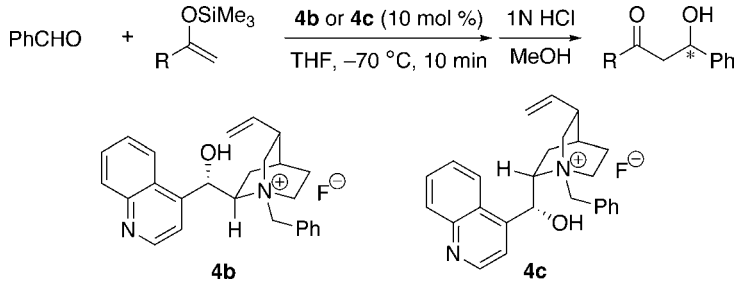
Campagne and Bluet recently reported the catalytic asymmetric vinylogous Mukaiyama aldol (CAVM) reaction of aldehydes with dienol silyl ether **15** using chiral ammonium fluorides as an activator. For example, the CAVM reaction of isobutyraldehyde with **15** in the presence of 10 mol% of **4b** in THF at room temperature led to the formation of the vinylogous aldol product **16** in 70% yield with 20% ee. The ee-value was improved to 30% by conducting the reaction at 0 °C (Scheme 9.6) [16].

Corey and Zhang utilized chiral quaternary ammonium fluoride **4d** possessing a 9-anthracenylmethyl group on nitrogen for the face-selective nitroaldol reaction of nitromethane with protected (*S*)-phenylalaninal. This was directed toward the



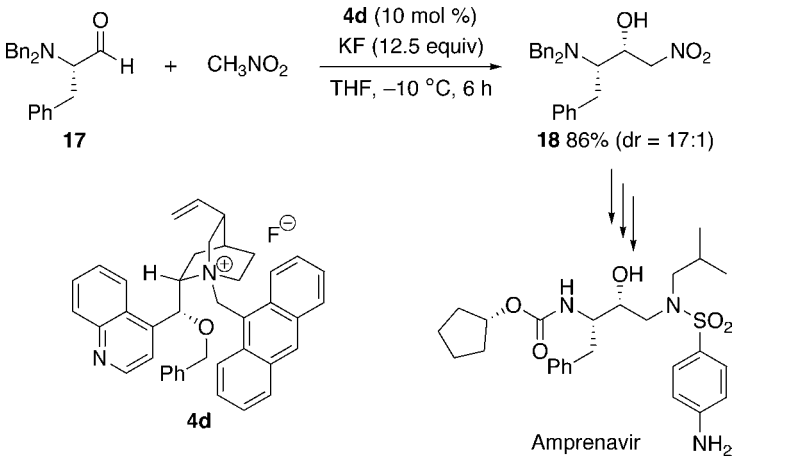
Scheme 9.6

Table 9.3 Asymmetric aldol reactions of enol silyl ethers with benzaldehyde catalyzed by chiral quaternary ammonium fluorides **4b** or **4c**.

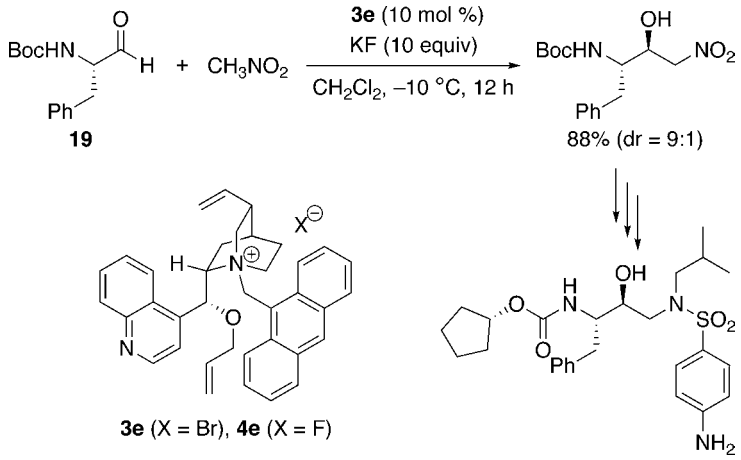


Entry	Catalyst	R	Yield (%)	*ee* (%)
1	**4b**	Ph	76	39.5 (*S*)
2	**4c**	Ph	46	35.5 (*R*)
3	**4b**	*p*-Cl-C_6H_4	55	42 (*S*)
4	**4b**	*p*-MeO-C_6H_4	70	36.5 (*S*)
5	**4b**	*t*-Bu	62	62 (*S*)
6	**4c**	*t*-Bu	55	39 (*R*)

practical stereoselective synthesis of amprenavir [17], an important second-generation HIV protease inhibitor with a number of clinical advantages over first-generation agents. A THF solution of *N*,*N*-dibenzyl-(*S*)-phenylalaninal (**17**) was added to a mixture of **4d**, nitromethane, and finely ground KF in THF at −10 °C (Scheme 9.7). When the mixture had been stirred for 6 h, the desired nitro alcohol **18** was isolated in



Scheme 9.7



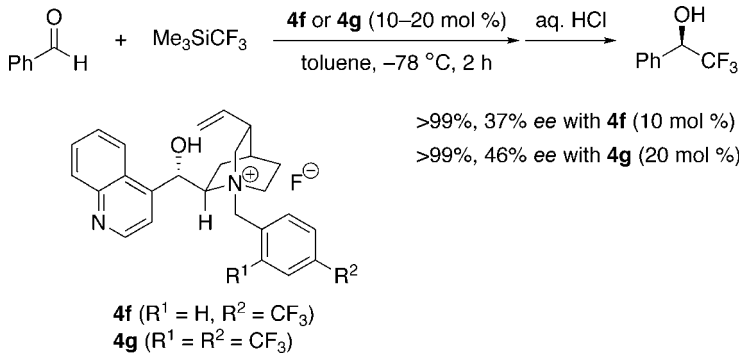
Scheme 9.8

86% yield with a diastereomeric ratio of 17 : 1, from which amprenavir was synthesized in a five-step sequence [18].

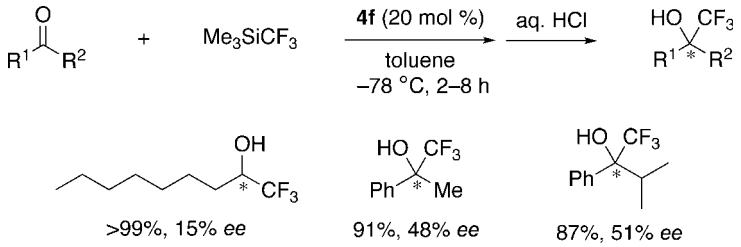
The asymmetric synthesis of the C(2) diastereomer of amprenavir was also accomplished, similarly starting from *N-tert*-butoxycarbonyl-(*S*)-phenylalaninal (**19**), where the requisite chiral ammonium fluoride **4e** was generated *in situ* from the corresponding bromide **3e** in the initial nitro aldol process (Scheme 9.8) [18].

Iseki, Nagai, and Kobayashi prepared cinchonine-derived **4f** and **4g** from the corresponding bromides by the method B (Scheme 9.5), and realized the asymmetric trifluoromethylation of aldehydes and ketones with trifluoromethyltrimethylsilane (Me_3SiCF_3) catalyzed by these ammonium fluorides (Schemes 9.9 and 9.10) [19]. Although the enantioselectivities are not sufficiently high, this reaction system should offer a new access to various chiral trifluoromethylated molecules of analytical and medicinal interests through appropriate modifications.

The hydrosilylation of carbonyl compounds with polymethylhydrosiloxane (PMHS) or other alkoxysilanes can be catalyzed by TBAF with high efficiency [20]. The asymmetric version of this process has been developed by Lawrence and

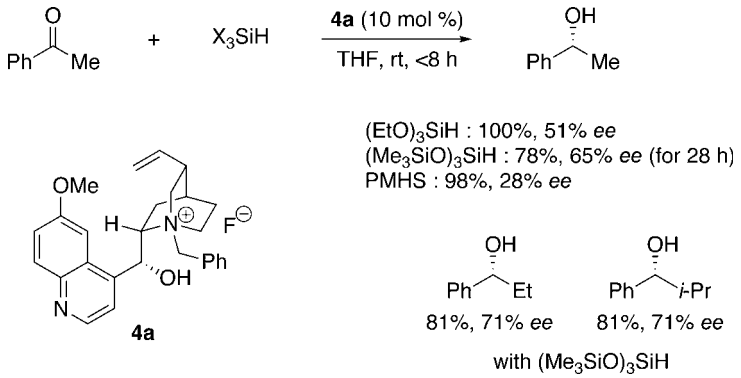


Scheme 9.9



Scheme 9.10

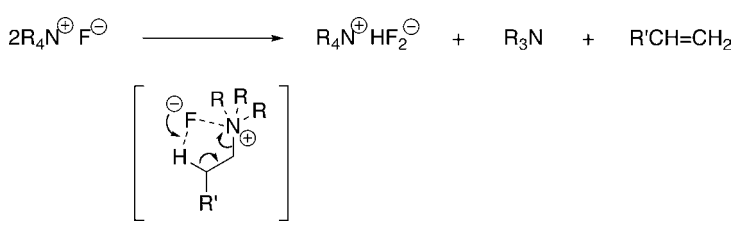
coworkers, using chiral ammonium fluorides **4** prepared *via* method C [21]. The reduction of acetophenone was performed with triethoxysilane (1.5 equiv.) and 10 mol% of **4a** in THF at room temperature, giving phenethyl alcohol quantitatively with 51% *ee* (*R*) (Scheme 9.11). In the reduction of propiophenone, a slightly higher enantioselectivity was observed. When tris(trimethylsiloxy) silane was used as a hydride source, the enantioselectivity was increased, although a prolonged reaction time was required. Although a significant rate acceleration was observed with PMHS, the stereoselectivity was unfortunately decreased.



Scheme 9.11

9.4
Chiral Quaternary Ammonium Bifluorides: Preparation and Use as Organocatalysts for Asymmetric Carbon–Carbon Bond-Forming Reactions

Tetraalkylammonium fluoride ($R_4N^+F^-$) is well known as being highly receptive to protic compounds such as hydrogen halides and water, affording non-stoichiometric hydrogen-bonded adducts, $R_4N^+F^-(HY)_n$, in non-polar solvents. This property reasonably accounts for the hygroscopic nature of ammonium fluorides. However, under strictly anhydrous conditions, intramolecular interactions are predominant and result in self-destruction of the tetraalkylammonium cation *via* Hoffman elimination to furnish tetraalkylammonium bifluoride, trialkylamine, and olefin (Scheme 9.12) [22]. Consequently, the resulting tetraalkylammonium bifluoride,

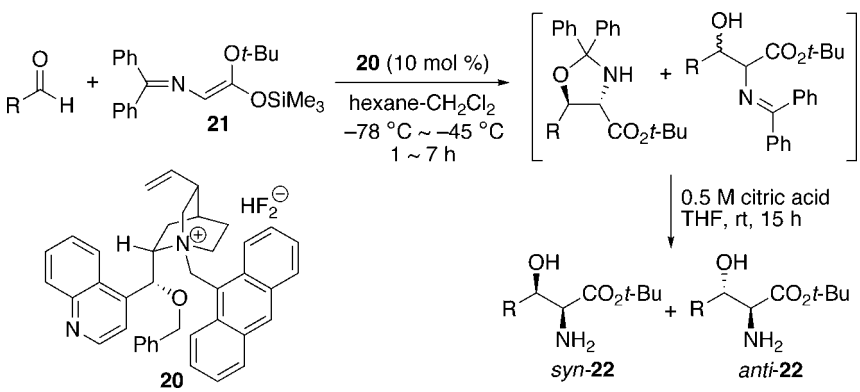


Scheme 9.12

$R_4N^+HF_2^-$, is more stable than the parent fluoride and is expected to be easy to handle, though its reactivity and selectivity in organic synthesis have scarcely been investigated, especially in the field of asymmetric catalysis.

Recently, Corey and coworkers prepared the cinchonidine-derived bifluoride **20** from the corresponding bromide by passage of a methanolic solution through a column of Amberlyst A-26 OH^- form, and subsequent neutralization with 2 equiv. of 1 N HF solution and evaporation (the modified method C in Scheme 9.5). The catalytic activity and chiral efficiency of **20** (dried over P_2O_5 under vacuum) have been demonstrated by the development of a Mukaiyama-type aldol reaction of ketene silyl acetal **21** with aldehydes under mild conditions, giving mostly *syn*-β-hydroxy-α-amino esters **22** as the major diastereomer with good to excellent enantiomeric excesses (Table 9.4) [23].

Table 9.4 Asymmetric Mukaiyama-type aldol reactions of a glycine derivative catalyzed by chiral quaternary ammonium bifluoride **20**.

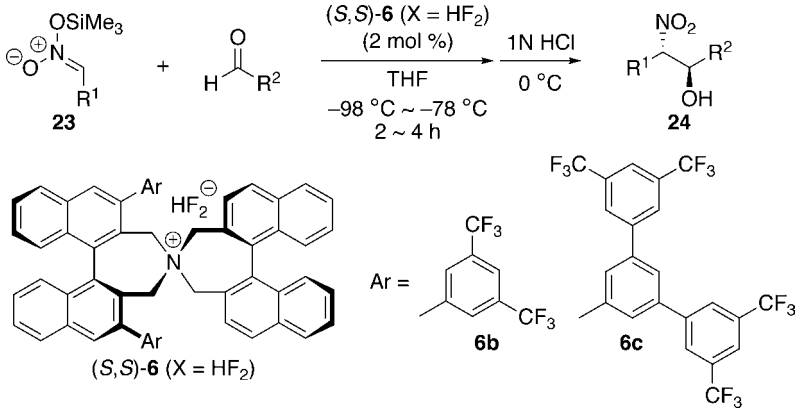


Entry	R	Yield (%)	*syn*/*anti*	*ee* (%) (*syn*/*anti*)
1	*i*-Pr	70	6:1	95/83
2	*c*-Hex	81	13:1	88/46
3	*n*-Hex	79	3:1	89/91
4	$Cl(CH_2)_3$	48	1:1	82/86
5	$Ph(CH_2)_2$	64	1:1	72/86
6	*i*-Bu	61	3:1	76/70

The nitroaldol reaction of silyl nitronates with aldehydes promoted by ammonium fluorides, which was originally introduced by Seebach and Colvin in 1978 [24], is a useful method for the preparation of 1,2-functionalized nitroalkanols. Recently, the present authors have succeeded in developing an asymmetric version of high efficiency and stereoselectivity by using a designer chiral quaternary ammonium bifluoride of type **6** as catalyst, which was readily prepared from the corresponding bromide by the modified method C in Scheme 9.5 [25].

Initial investigations showed that the treatment of trimethylsilyl nitronate **23a** (R^1 = Me) with benzaldehyde (R^2 = Ph) in the presence of (*S*,*S*)-**6b** (X = HF_2, 2 mol %) in THF at −98 °C for 1 h and at −78 °C for 1 h and subsequent hydrolysis with 1 M HCl at 0 °C, resulted in clean formation of the corresponding nitroalkanol **24** (R^1 = Me, R^2 = Ph) in 83% yield (*anti*/*syn* = 74 : 26) with 33% *ee* (*anti* isomer) (entry 1 in Table 9.5). Notably, the poor diastereo- and enantioselectivities were dramatically improved by switching the catalyst to (*S*,*S*)-**6c** (X = HF_2) possessing a radially extended 3,3-aromatic substituent (Ar), and **24** (R^1 = Me, R^2 = Ph) was obtained in 92% yield (*anti*/*syn* = 92 : 8 with 95% *ee* (*anti* isomer) (Table 9.5, entry 2). This asymmetric nitroaldol protocol tolerates various aromatic aldehydes to afford *anti*-nitroaldols selectively, being complementary to Shibasaki's method

Table 9.5 Asymmetric nitroaldol reactions catalyzed by chiral quaternary ammonium bifluorides **6**.



Entry	Catalyst	R^1	R^2	Yield (%)	*anti*/*syn*	*ee* (%) (*anti*)
1	**6b**	Me	Ph	83	74:26	33
2	**6c**	Me	Ph	92	92:8	95
3	**6c**	Me	*p*-Me-C_6H_4	92	94:6	97
4	**6c**	Me	*p*-F-C_6H_4	94	83:17	90
5	**6c**	Me	β-Np	88	92:8	93
6	**6c**	Et	Ph	94	90:10	91
7	**6c**	$BnO(CH_2)_2$	Ph	70	87:13	91

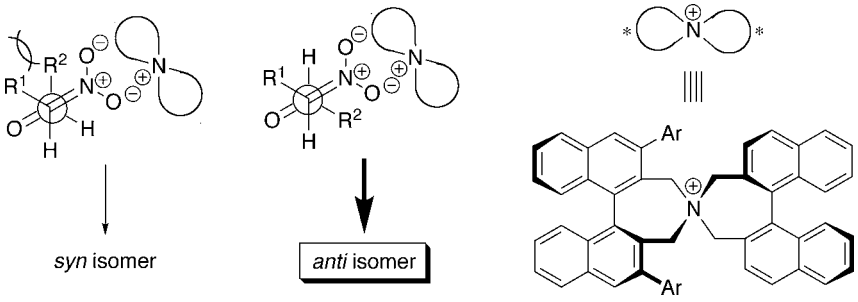
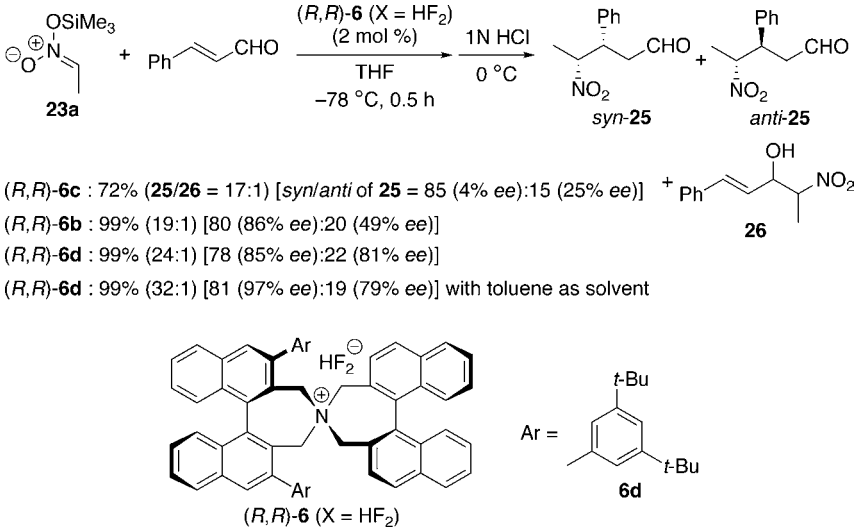


Figure 9.1 Plausible transition-state model for nitroaldol reactions

using heterobimetallic complexes that gives *syn*-nitroaldols as the major products [26].

The observed high *anti* selectivity may reflect the acyclic extended transition-state mechanism postulated in the fluoride-catalyzed reactions (Figure 9.1) [27]. Judging from the product configuration, chiral ammonium cation should effectively cover the *si*-face of the nitronate and the selective approach of aldehyde from the *re*-face should result.

During the course of studies on these asymmetric nitroaldol reactions catalyzed by chiral ammonium bifluorides **6** ($X = HF_2$), the reaction of **23a** was attempted with *trans*-cinnamaldehyde, a representative α,β-unsaturated aldehyde, under the influence of (*R*,*R*)-**6c** ($X = HF_2$, 2 mol%) in THF at −78 °C. The starting aldehyde was consumed within 30 min at this temperature and, surprisingly, the 1,4-addition product **25** was obtained predominantly as a diastereomeric mixture with concomitant formation of the initially expected nitroaldol (1,2-addition product) **26** [72% combined yield, **25**/**26** = 17 : 1, *syn*/*anti* of **25** = 85 (4% *ee*):15 (25% *ee*)] (Scheme 9.13).

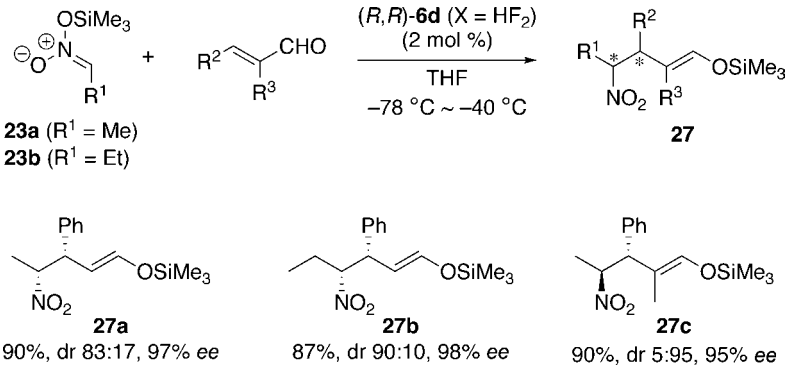


Scheme 9.13

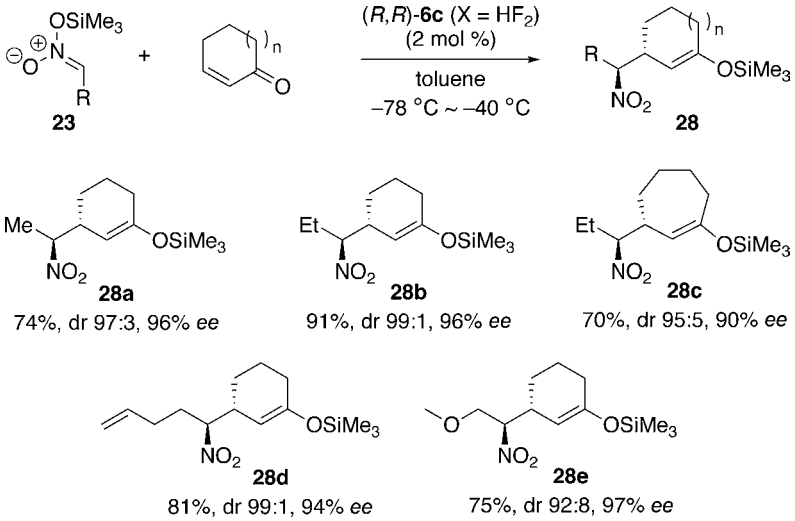
It should be noted that achiral TBAF gave rise to a mixture of **25** and **26** in a ratio of 1.1 : 1 (76% yield, *syn*/*anti* = 61 : 39 for **25**). Although the observed enantiomeric excesses were still low at this stage, these results strongly implied that both regio- and stereochemistry of the fluoride-catalyzed addition of silyl nitronates to α,β-unsaturated aldehydes could be precisely controlled by a designer chiral quaternary ammonium bifluoride of type **6** *via* the *in-situ* formation of chiral ammonium nitronates. This would in turn allow direct access to optically active γ-nitro aldehydes, which are very useful precursors of various complex organic molecules, including aminocarbonyls. This should also provide a unique, yet powerful, strategy for achieving the hitherto difficult catalytic asymmetric Michael addition to α,β-unsaturated aldehydes [28].

From this standpoint, a thorough examination was conducted of the effect of the catalyst substituent (Ar) and reaction conditions on the reactivity and selectivity of this procedure. As also shown in Scheme 9.13, the sterically less-congested (*R*,*R*)-**6b** (X = HF_2) exerted a high catalytic activity, affording the products quantitatively with high regio- and diastereoselectivity (**25**/**26** = 19 : 1, *syn*/*anti* of **25** = 80 : 20), and the enantioselectivity of the major *syn*-**25** was drastically improved to 86% ee. Further, **25** was obtained with even higher regioselectivity and comparable stereoselectivity when the catalyst (*R*,*R*)-**6d** (X = HF_2) having the 3,5-di-*tert*-butylphenyl substituent was employed. Moreover, the use of toluene as solvent led to an almost exclusive formation of the 1,4-adduct (**25**/**26** = 32 : 1) with similar diastereoselectivity (*syn*/*anti* = 81 : 19), and critical enhancement of the enantioselectivity was attained (97% *ee*) [29].

The significant synthetic advantage of this approach is the isolation of regio- and stereo-defined enol silyl ethers of optically active γ-nitro aldehydes as an attractive Mukaiyama donor, not readily accessible by ordinary asymmetric methodologies (Scheme 9.14). For example, after the reaction of silyl nitronate **23a** with *trans*-cinnamaldehyde under optimized conditions, the resulting mixture can be directly purified by silica gel column chromatography to give the optically active enol silyl ether **27a** in 90% yield. High levels of catalytic efficiency and stereoselectivity were also available in the Michael addition of silyl nitronate **23b**. The introduction of an alkyl substituent at the α-carbon of enals can be well accommodated, as excellent



Scheme 9.14



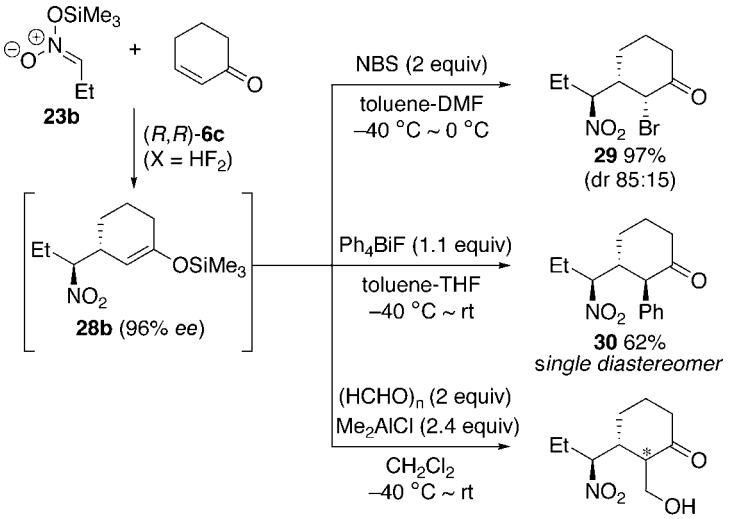
Scheme 9.15

diastereo- and enantio facial differentiation have been achieved with α-methyl-*trans*-cinnamaldehyde [29].

As an extension of this highly enantioselective Michael addition of silyl nitronates with α,β-unsaturated aldehydes, the reactions with cyclic α,β-unsaturated ketones as a Michael acceptor were also tested (Scheme 9.15). Cyclohexenone and cycloheptenone were employed as a useful Michael acceptor with various silyl nitronates in the presence of catalyst (*R,R*)-**6c**, and gave the corresponding enol silyl ethers **28** with excellent stereoselectivities [30].

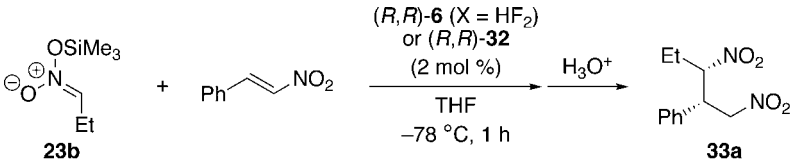
The versatility of the optically active enol silyl ethers **28** in synthetic chemistry serves as a stimulus for any exploration of the potential application of this methodology. Accordingly, one-pot, stereoselective transformations of **28** to the corresponding α-substituted γ-nitro ketones having three consecutive stereocenters were established (Scheme 9.16). The generation of **28b** by the chiral quaternary ammonium bifluoride (*R,R*)-**6c** (X = HF_2)-catalyzed Michael addition of **23b** to cyclohexenone at −40 °C, followed by the addition of *N,N*-dimethylformamide as a polar co-solvent and *N*-bromosuccinimide and continuous stirring at 0 °C for 30 min resulted in the production of α-brominated product **29** in 97% yield. The one-pot α-phenylation was also achieved with fluorotetraphenylbismuth (Ph_4BiF) [31] to afford **30** in 62% yield, with complete diastereocontrol. Furthermore, a dimethylaluminum chloride-mediated reaction with paraformaldehyde appeared feasible, giving rise to a hydroxymethylcyclohexanone derivative **31** as a single diastereomer (52%) [30].

Further applications of the chiral ammonium bifluoride-catalyzed enantioselective Michael addition of silyl nitronates has been shown in the reactions with nitroalkenes as a Michael acceptor (Scheme 9.17). These studies were started by examining the reaction of nitropropane-derived silyl nitronate **23b** with β-nitrostyrene, using the chiral quaternary ammonium bifluoride (*R,R*)-**6d**. When β-nitrostyrene was treated with **23b** (1.2 equiv.) in the presence of (*R,R*)-**6d** (2 mol%) in THF at −78 °C, the

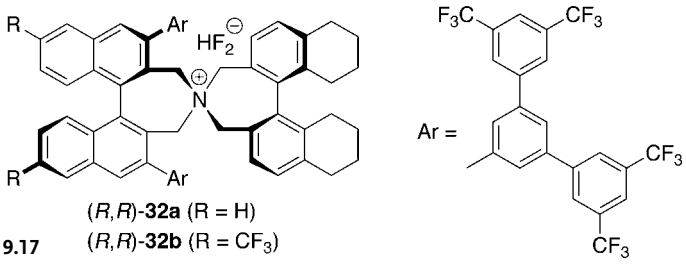


Scheme 9.16

desired product **33a** was obtained in 73% yield with 29% *ee*. On the basis of this result, the effect of the catalyst structure was evaluated. Although the electron-withdrawing 3,5-bis(trifluoromethyl)phenyl-substituted (*R,R*)-**6b** exhibited comparable chiral efficiency to that of (*R,R*)-**6d**, modification of the 3,3-aromatic substituent to the *meta*-

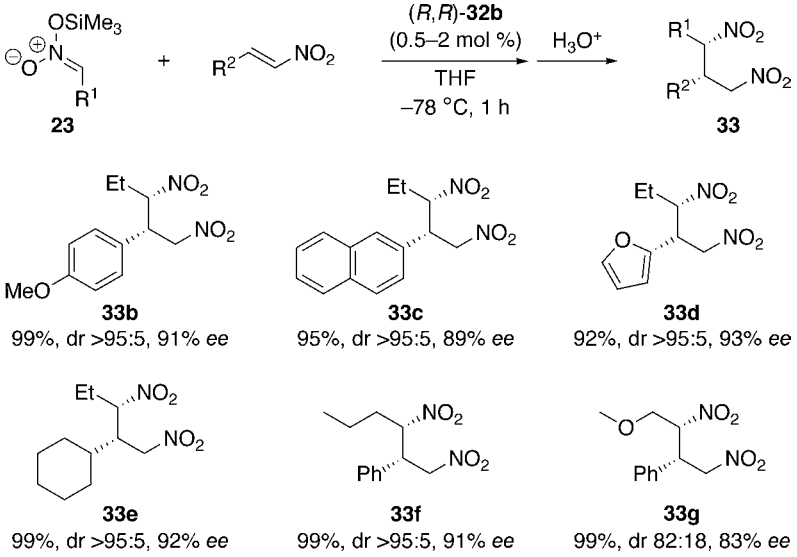


(*R,R*)-**6d** : 73%, *syn*/*anti* = >95:5, 29% *ee*
(*R,R*)-**6b** : 67%, *syn*/*anti* = >95:5, 32% *ee*
(*R,R*)-**6c** : 80%, *syn*/*anti* = >95:5, 80% *ee*
(*R,R*)-**32a** : 78%, *syn*/*anti* = >95:5, 89% *ee*
(*R,R*)-**32b** : 85%, *syn*/*anti* = >95:5, 91% *ee*



(*R,R*)-**32a** (R = H)
(*R,R*)-**32b** (R = CF_3)

Scheme 9.17

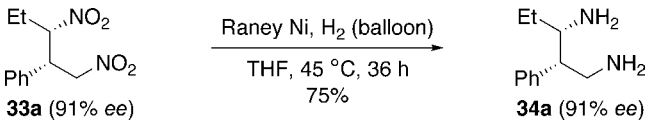


Scheme 9.18

terphenyl-type structure (*R,R*)-**6c** led to a dramatic improvement in selectivity. Furthermore, the chiral ammonium bifluoride (*R,R*)-**32a** was assembled; this consisted of a chiral octahydrobinaphthyl subunit, with the expectation that its steric and electronic effects would help to control stereoselectivity. Fortunately, the conjugate addition of **23b** to β-nitrostyrene proceeded smoothly under the influence of (*R,R*)-**32a** in a highly diastereoselective manner, affording *syn*-**33a** in 78% yield with 89% *ee*. Moreover, the introduction of a trifluoromethyl group in the 6,6′ position of the binaphthyl core of (*R,R*)-**32b** delivered even higher enantioselectivity (91% *ee*) [32].

Having established the optimized conditions, the scope of the reaction was investigated using silyl nitronate **23b** and a variety of nitroalkenes (Scheme 9.18). The reaction of nitroalkenes having aromatic, heteroaromatic and alkyl groups gave the corresponding products **33** with good diastereo- and enantioselectivities. The present method was applicable to other silyl nitronates derived from simple nitroalkanes, where eminent catalytic activity and a high level of stereoselectivity were also attained.

The resulting 1,3-dinitro compounds with two consecutive stereochemically defined stereocenters can be readily converted into the corresponding 1,3-diamines, which are versatile chiral building blocks from synthetic as well as pharmaceutical viewpoints (Scheme 9.19).



Scheme 9.19

9.5 Conclusions

Currently, it is fair to say that asymmetric synthesis using chiral quaternary ammonium fluorides remains an underdeveloped field, and the various useful stereoselective carbon–carbon bond-forming processes described in this chapter are only the start of an exploration of the vast synthetic potential of this process, particularly when combined with current knowledge of organosilicon chemistry. It seems that the key issue to be addressed is the rational molecular design of chiral quaternary ammonium cations with appropriate steric and electronic properties. These are expected to be readily tunable to impart not only a sufficient reactivity but also an ideal chiral environment to the requisite nucleophile involved in a desired chemical transformation. Clearly, the continuous accumulation of information related to the structure of fluoride salts and their reactivity and selectivity should create a solid basis for this field, offering – in time – a unique yet reliable tool for sophisticated bond construction events with rigorous stereocontrol, under mild conditions.

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